Department of Neurosurgery
Helsinki University Central Hospital

Doctoral Program of Clinical Research
University of Helsinki, Helsinki, Finland

HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH BRAIN ARTERIOVENOUS MALFORMATION

Anni Pohjola

ACADEMIC DISSERTATION

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Author's contact information
Anni Pohjola, MD
Department of Neurosurgery
Topeliuksenkatu 5B
00260 Helsinki, Finland
anni.pohjola@hus.fi
mobile: +358 40 524 8970

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Supervisors

Professor Aki Laakso, MD, PhD
Department of Neurosurgery, Oulu University Hospital, Finland
University of Oulu

Professor Mika Niemelä, MD, PhD
Department of Neurosurgery, Helsinki University Hospital, Finland
University of Helsinki

Faculty representative

Docent Martin Lehecka, MD, PhD
Department of Neurosurgery, Helsinki University Hospital, Finland

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Department of Neurosurgery, Kuopio University Hospital
University of Eastern Finland, Finland

Professor Pekka Jäkälä, MD, PhD
Department of Neurology, Kuopio University Hospital
University of Eastern Finland, Finland

Opponent

Professor Karl Schaller, MD
Division of Neurosurgery, Department of Clinical Neurosciences,
Geneva University Hospitals, Geneva, Switzerland
President, the European Association of Neurosurgical Societies (EANS)

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ABSTRACT

Brain arteriovenous malformations (AVM) are rare vascular anomalies in which the cerebral arteries and veins are connected without the normal intervening capillary bed. Most often, in roughly half of the cases, the event leading to diagnosis is intracranial hemorrhage. The second most common symptom is a focal epileptic seizure, leading to diagnosis in one-third of the cases. AVM incidence in the general population is approximately 1/100,000 person-years. The average age for AVM diagnosis is slightly over 30 years, meaning that the disease often affects working-age people. It is also a significant cause of intracranial hemorrhage in children and young adults. The AVM hemorrhage is lethal in, on average, 5–25% of patients.

In this thesis we have studied patients in the Helsinki AVM database using the 15D health-related quality of life (HRQoL) instrument and questionnaire data about lifestyle. Our database consists of 805 AVM patients treated in the Helsinki University Hospital Department of Neurosurgery between 1942 and 2014. Of them, 325 patients answered the mailed questionnaire sent in 2016 and comprise the study cohort of this thesis. Our research revealed that after a mean 17.6 years (SD ±12.0 yr) of follow-up the HRQoL of treated AVM patients in general was, when considering the difficulty of the disease, only modestly decreased. Also, most of the patients had been able to return to work. In the multivariate model, the decreased HRQoL of AVM patients was explained by older age, sex (being female), difficult refractory epilepsy, difficult location or structure of the AVM, and more than one hemorrhagic episode. Our results support active AVM treatment in those cases which the procedure can be done safely and the treatment-related risks do not exceed the estimated cumulative rupture risk. Another novel finding from our study cohort was that the prevalence of smokers was significantly higher in AVM patients when compared to a matched general population. The high prevalence, especially during the diagnosis, inspires more vigorous investigation of the role of cigarette smoking in the currently unknown etiology of AVMs. With our final article, we participated in the on-going discussion in the scientific community about the statistical handling of the commonly used functional outcome instrument, the modified Rankin Scale. We showed, using our AVM patient cohort, that the popular dichotomous approach in outcome assessment could significantly bias research results.

TIIVISTELMÄ

Aivojen valtimolaskimoepämuodostumat (AVM) ovat harvinaisia verisuoniepämuodostumia, joissa aivovaltimot ja -laskimot ovat yhdistyneet ilman normaalia hiussuoniverkostoa. Diagnoosiin useimmiten, noin puolessa tapauksista, johtava syy on aivoverenvuoto. Toiseksi yleisimmin diagnoosiin johtaa epileptinen kohtaus, noin kolmanneksella potilaista. AVM:ien ilmaantuvuus väestössä on keskimäärin 1/100 000 henkilövuotta. Keskimäärin AVM diagnosoidaan hieman yli 30-vuotiailla. Sairaus koskettaakin usein työikäisiä ja se on yksi merkittävistä lasten ja nuorten aikuisten aivoverenvuodon aiheuttajista. Potilaista, joilla AVM puhkeaa, aivoverenvuoto johtaa kuolemaan noin 5–25%:ssa tapauksista.

Tässä väitöskirjatyössä on tutkittu Helsinki AVM -aineiston potilaita käyttäen 15D-elämänlaatumittaria ja kyselykirjeitse saatua dataa liittyen potilaiden elintapoihin. Tietokantaamme on kerätty vuosina 1942–2014 Helsingin yliopistollisen sairaalan Neurokirurgian klinikassa hoidetut AVM-potilaat (n=805). Heistä 325 vastasi vuonna 2016 lähetettyyn elämänlaatukyselykirjeeseen ja muodostaa tämän väitöskirjan päätutkimuskohortin. Tutkimuksemme paljasti, että keskimäärin 17.6 vuoden (SD=±12.0v) seuranta-ajan jälkeen hoidettujen AVM-potilaiden elämänlaatu oli, ottaen huomioon taudin vaikeusasteen, ainoastaan maltillisesti madaltunut. Lisäksi, suurin osa potilaista oli kyennyt palaamaan työelämään. Monimuuttujamallissa heikentynyttä elämänlaatua selittäviä tekijöitä AVM-potilaiden välillä olivat vanhempi ikä, naissukupuoli, vaikea jäännösepilepsia, AVM:n vaikea anatominen sijainti tai rakenne, ja useampi kuin yksi aivoverenvuoto. Tutkimustuloksemme kannustavat AVM:n aktiiviseen hoitoon niissä tapauksissa, joissa toimenpide voidaan suorittaa turvallisesti, eivätkä toimenpiteen riskit ylitä arvioitua elinaikana kertyvää vuotoriskiä. Toinen uusi löydös tutkimuskohortistamme oli, että tupakoivien AVM-potilaiden esiintyvyys on huomattavasti korkeampi kuin tupakoijien osuus suomalaisessa verrokkiväestössä. Erityisesti tupakoijien suuri määrä AVM:n diagnoosivaiheessa kannustaa tutkimaan tupakoinnin osuutta AVM:ien nykyhetkellä tuntemattomassa etiologiassa. Lopulta, otimme tutkimuksellamme kantaa tiedeyhteisössä käytävään keskusteluun yleisesti käytetyn modified Rankin Scale -luokituksen tilastollisesta käsittelystä. Osoitimme käyttämällä AVM-potilailtamme saatua 15D-elämänlaatudataa, että tutkimuksissa usein käytetty kahtiajakoon pohjautuva luokittelu saattaa merkittävästi vääristää tutkimustuloksia.

LIST OF ORIGINAL PUBLICATIONS

The thesis consists of three original research articles:

I. Pohjola A, Oulasvirta E, Roine RP, Sintonen HP, Hafez A, Koroknay-Pál P, Lehto H, Niemelä M, Laakso A. Long-term health related quality of life in 262 patients with brain arteriovenous malformation. Neurology. 2019 Oct1;93(14):e1374-e1384.

II. Pohjola A, Lindbohm JV, Oulasvirta E, Hafez A, Koroknay-Pál P, Laakso A, Niemelä M. Cigarette smoking is more prevalent in patients with brain arteriovenous malformation compared to general population: A Cross-Sectional Population-Based Study [published online ahead of print, 2020 Jul 20]. Neurosurgery. 2020;nyaa281. doi:10.1093/neuros/nyaa281

III. Pohjola A, Oulasvirta E, Roine RP, Sintonen HP, Hafez A, Koroknay-Pál P, Lehto H, Niemelä M, Laakso A. Comparing health-related quality of life in modified Rankin Scale grades. *Acta Neurochirurgica, in review.*

The articles are referred to in the text using Roman numerals. They are reprinted here with the permission of the publisher. Additionally, some unpublished data is presented.

ABBREVIATIONS

AED	Anti-epileptic drug
ANCOVA	Analysis of covariance
ARUBA	A Randomized trial of Unruptured Brain Arteriovenous malformations
aSAH	Aneurysmal subarachnoid hemorrhage
AVM	Brain arteriovenous malformation
AQoL	Assessment of Quality of Life
CI	Confidence interval
CRSR	Cumulative relative survival ratio
CT	Computed tomography
CTA	Computed tomographic angiography
DAVF	Dural arteriovenous fistula
DSA	Digital subtraction angiography
ERK	Extracellular signal-regulated kinases
EQ-5D	EuroQol-5D
HRQoL	Health-related quality of life
HHT	Hereditary hemorrhagic telangiectasia
HUH	Helsinki University hospital
HUI	Health Utilities Index
IA	Intracranial aneurysm
ICG	Indocyanine green videoangiography
ICH	Intracerebral hemorrhage
IS	Ischemic stroke
IVH	Intraventricular hemorrhage
MAPK	Mitogen-activated protein kinases
MD	Mean difference
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
mRNA	Messenger RNA
mRS	Modified Rankin Scale
OR	Odds ratio
PICH	Primary intracerebral hemorrhage
QoL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
RSR	Relative survival ratio
SAH	Subarachnoid hemorrhage

SD	Standard deviation
SDH	Subdural hemorrhage
SF-36	Short form 36
SPC	Spetzler-Ponce grade
SRS	Stereotactic radiosurgery
SRT	Stereotactic radiotherapy
SMG	Spetzler-Martin grade
TOBAS	Treatment Of Brain AVMS
tPA	Tissue plasminogen activator
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

1 INTRODUCTION

1.1 Brain arteriovenous malformations

Brain arteriovenous malformations (AVMs) are rare vascular anomalies of unknown etiology. Owing to their complex neurovascular anatomy, they are one of the most difficult neurosurgical diseases to manage. AVM consists of a tangle of vessels called a nidus, with abnormal connections between the arteries and veins without a capillary network in between.[1] AVMs are most often detected with rupture; however, epileptic seizures or a neurological deficit might also lead to diagnosis.[2] The intracranial hemorrhage caused by AVM rupture is associated with significant mortality and morbidity.[3] This is especially distressing since the patients are mostly working-age, young adults and children.[4] Considering the young age of AVM patients, it is often meaningful to try eliminating the risk of AVM rupture altogether with interventional treatment.[5] However, the risks related to the procedure itself are also notable. They can pose too large a risk of complications and therefore some AVMs can only be observed.[6] Fortunately, novel medical therapies are being developed and this noninvasive approach might revolutionize the treatment of AVMs in the future.[7]

1.2 Helsinki AVM database

The Helsinki AVM database has been collected retrospectively from medical records and images. It consists of all AVM patients in the Helsinki University Hospital (HUH) catchment area who were treated between 1942 and 2014 in our neurosurgical clinic. At the time of working on this thesis, the database consisted of 805 patients. In 2016, questionnaire letters were sent to all adult patients in the database. These letters included a separate panel of questions regarding self-sufficiency and lifestyle, and the 15D health-related quality of life (HRQoL) questionnaire. The patients who returned the questionnaire were collected into a HRQoL database, which consists of 325 living adult AVM patients. The patients in this database were the main study population of this thesis project

2 REVIEW OF THE LITERATURE

2.1 Brain arteriovenous malformations

2.1.1 Anatomy

AVMs are rare vascular anomalies located inside the cranium. They are made of an abnormal collection of vessels where a draining vein receives oxygenated blood from a feeder artery without the normal interposed capillary beds. The blood flow goes through a tangle of blood vessels, called a nidus (Figure 1).[1] The nidus consists of direct connections between the arterial and the venous side which act as high-flow shunts wherein the medium-to-high pressure arterial blood flowing to the draining veins creates a risk of rupture. An AVM rupture leads to an intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), intraventricular hemorrhage (IVH), subdural hemorrhage (SDH) or a combination of these.[8] The most common type is ICH, accounting for approximately 80% of the ruptures.[9] AVMs can be classified based on their anatomical characteristics. These classifications can be used to estimate the rupture risk of the lesion, the anticipated treatment effect, and the short- and long-term outcomes, and are vital in the preoperative understanding of the topography and angioarchitecture. Topographically, AVMs are classified as either telencephalic (so-called cortical AVMs, 72% of the lesions), subcortical (2%), or deep / central AVMs (26%).[1] The

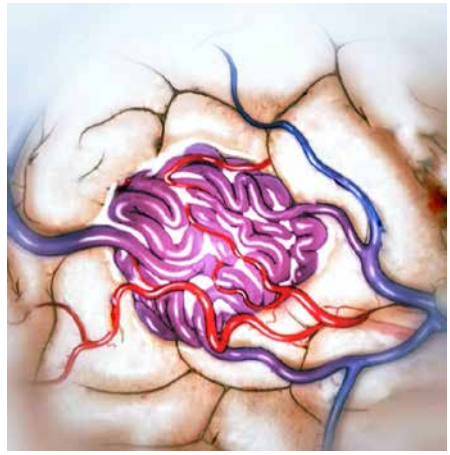

Figure 1. A schematic illustration of a cortical brain AVM.

most common type, the cortical AVMs, can be located in the sulci (28%), gyri (12%) or mixed sulco-gyrally (29%).[1] In addition to this, location in regard to the tentorium determines whether AVM is supratentorial (86%) or infratentorial (14%).[10, 11] The eloquence is another determining factor of location. Eloquent locations include the functionally important structures of the cerebral lobe and the vitally important structures such as the brainstem and midbrain. The feeding arteries can be subdivided into several categories depending on their origin. Generally speaking, the superficial arteries are often easier to occlude during surgery, whereas the feeders from perforator arteries can create significant challenges.[12] Venous drainage can be subdivided into deep or superficial draining, depending on the location of the veins involved in the nidus. Superficial drainage through the cortical

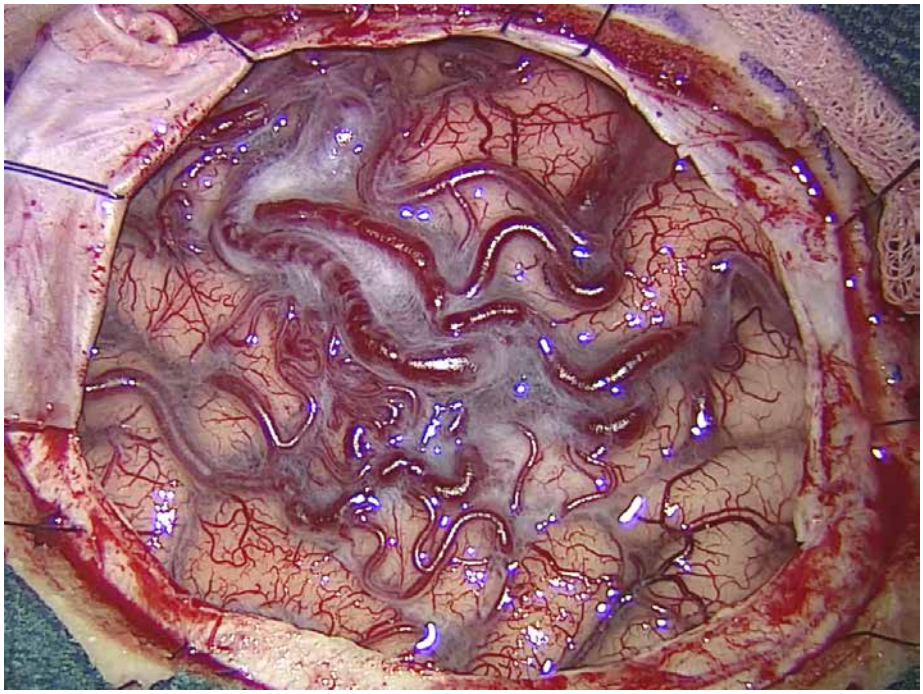

Figure 2. Intraoperative picture of a cortical brain AVM.

veins often drains into the adjacent dural sinus, whereas deep AVMs drain into the subependymal venous system. The size of the AVM is determined by the size of the nidus and can vary from a couple of millimeters to multiple centimeters wide. In around 7% of cases, there is an associated flow-related aneurysm, a pouch-like widening of an artery, located near the AVM commonly in the feeder artery.[13]

2.1.2 Development and pathophysiology

AVMs are classically viewed as congenital lesions which develop prenatally and in most cases remain silent until they become symptomatic, usually by the third or fourth decade of the patient's life.[14, 15] This view has been questioned with an increasing number of *de novo* AVMs reported and novel discoveries of the genetics behind the etiology.[7, 11, 16, 17] Furthermore, very few reports of prenatal AVMs exist,[18-20] and the diagnosis remains extremely rare during the first years after birth.[21, 22] Although there is an increasing body of evidence about the molecular mechanisms and genetics behind sporadic AVMs, the exact pathogenesis remains mostly unknown.[7, 23-26] Dysfunction of the cerebrovascular endothelium and the angiogenic pathways seem to play a major role in the formation based on current knowledge.[7, 27]

2.1.2.1 Related diseases

An autosomal dominantly inherited condition, Osler-Weber-Rendu syndrome or hereditary hemorrhagic telangiectasia (HHT), significantly increases the risk of developing AVMs.[28] In HHT this is caused by loss-of-function mutations in genes which encode the proteins mediating TGF-β signaling.[29, 30] HHT patients form a minority of AVM patients, as about 95% of AVMs are sporadic.[24, 31] Another closely related etiology, dural arteriovenous fistulae (DAVF), shares the same anatomic features as AVMs, with an arteriovenous shunt without an intervening capillary bed. The shunt, between meningeal arteries and dural sinus and/or cortical veins, is usually contained inside the leaflets of the dura mater, compared to AVMs which are inside the pia mater.[32] Most DAVFs in adulthood are acquired, and for a proportion of patients the etiology can be tracked down to a specific event (e.g., traumatic head injury, previous craniotomy, tumor or dural sinus thrombosis).[33, 34] A similar relationship has not been found in AVM patients. The formation of DAVFs is proposed to be related to either progressive stenosis or occlusion of dural venous sinuses, which leads to an increase in sinus venous pressure which in turn triggers the development of the fistulous connections between the meningeal arteries and the dural sinus or cortical veins.[34] This theory is supported by the finding of a correlation between DAVF patients and inherited thrombotic diseases, such as Factor V Leiden or protein C deficiency.[34, 35] Again, similar connections have not been reported in AVM patients.

2.1.2.2 Introduction to angiogenesis and the two-hit theory

During embryogenesis the brain vasculature is formed *de novo* from endothelial precursor cells, angioblasts, in a process called vasculogenesis.[36] After this, new blood vessels are formed from the pre-existing ones in angiogenesis.[37] Angiogenesis is also present after the developmental phases, postnatally, in many physiological processes such as wound healing and granulation tissue formation, and in pathological processes in which, for instance, a malignant tumor can create neovascularization to gain nutrients and oxygen.[38] After birth there are several angiogenic growth factors which control the changes in the body's vasculature by stimulating blood vessel formation and growth.[39] One of the most important angiogenic factors in the human brain is the vascular endothelial growth factor (VEGF).[36, 40] In addition, a number of inhibiting factors and extracellular proteins are involved in the cascade of physiological angiogenesis.[39] TGF-β, VEGF and many other growth factors, as well as signaling cascades such as NOTCH and RAS/MAPK/ERK, are involved in the regulation of target gene expression, and when mutated cannot up- or downregulate the desired genes.[41-43] These play a major role in the arteriovenous specification, and together with the downstream transcription factors and the external mutagens create the fundamentals behind the

pathophysiology of AVMs.[27, 44] A recent breakthrough in the research of sporadic AVMs was the finding of AVM endothelial cells having somatic mutations in KRAS, a proto-oncogene part of the Ras family of proteins associated with cell growth and proliferation.[7] This specific study also illustrated increased MAPK-ERK signaling in the samples without the KRAS variants, which the researchers concluded might delineate the importance of the MAPK-ERK pathway in AVM formation.[7]

General theories about the formation of brain vascular anomalies have been proposed. One of them suggests a two-hit theory, originally developed in cancer research, but which applies to many other diseases as well.[44] A rather simplified version of the theory proposes the first hit, a mutation, enables the pathological reactivation of pathways involved in cellular proliferation, apoptosis and abnormal tissue formation. However, we are constantly battling somatic mutations around our bodies, which is why the second hit is needed to keep the mutated pathways activated. The second hit adjusts the microenvironment by promoting cellular proliferation, differentiation and migration. The hit can be either another mutation which sustains the proinflammatory, promigratory and proliferative stimuli, or an external mutagen which maintains this abnormal microenvironment (Figure 3).[44]

2.1.3 Patient characteristics and epidemiology

AVMs often impair young patients in their third or fourth decade of life.[9, 45] However, many live asymptomatically

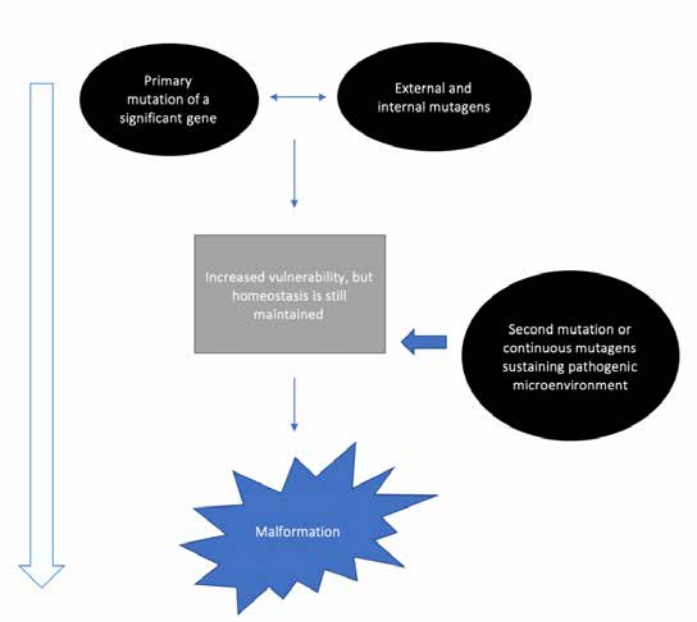

Figure 3. Illustration of the scheme behind the two-hit theory. The cascade begins with a first hit promoting a mutation to a key regulatory gene; however, this alone can be controlled by different cellular mechanisms and homeostasis is sustained. If, however, there is another key mutation or the pathogenic microenvironment is sustained by external factors, the second hit is able to destabilize the homeostasis and a malformation can develop.

without ever getting the diagnosis, which understandably complicates the prevalence determination.[46] The prevalence might be up to 0.2%,[4, 31] whereas patients with a confirmed AVM diagnosis only make-up 0.02% of the population.[12] The current incidence of AVMs is around 1/100,000 person-years, however, the incidence will supposedly slightly increase owing to more extensive imaging.[9, 46] AVM hemorrhages account for roughly 4% of all non-traumatic strokes.[47] Owing to their peak prevalence in the early decades of life, they account for one-third of all hemorrhagic strokes in young adults and by some estimates even half of the hemorrhagic strokes in children.[47–49] In our own database, there is a slight predominance of male patients compared to females, however, in the existing literature the distribution is equal.[47] (Figure 4).

2.1.4 Symptoms and diagnosis

AVMs most commonly present with ICH.[45, 50] AVM patients are typically younger than patients with other types of ICH – in a massive study consisting of 630,969 hospitalizations for ICH from 2002 to 2011 in the United States the mean age between AVM patients and other causes for ICH were 52 and 72 years, respectively.[51] In the same study, there was a slight male predominance, with 52.5% males versus 49.3% in other causes for ICH.[51] The other presenting symptoms of AVM patients are epileptic seizures, focal neurological deficits, headache, as well as other types of intracranial hemorrhages.[52] Epileptic seizures are more common in AVM patients than with other causes of ICH.[51]

The symptomatology depends on the location of the lesion, and therefore

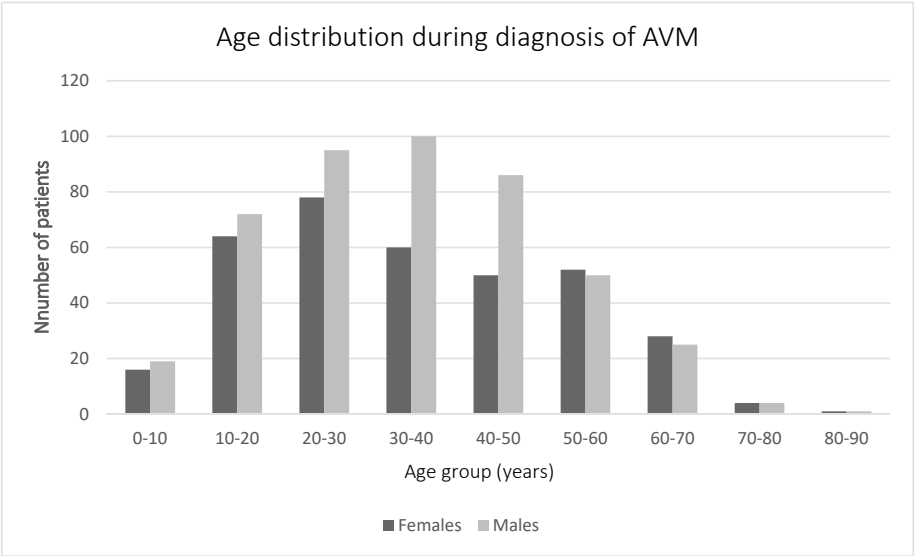

Figure 4. Age distribution at diagnosis of AVM based on our AVM database of 805 AVM patients.

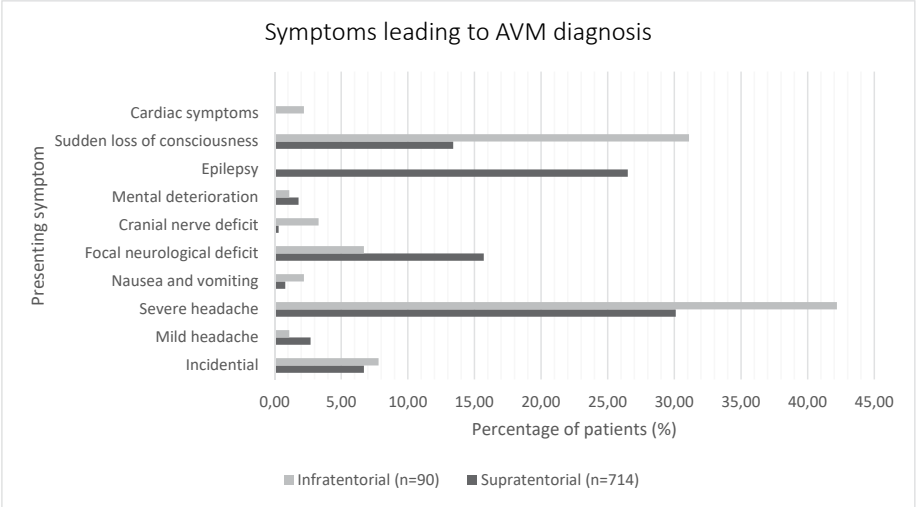

Figure 5. The distribution of symptoms in 805 AVM patients in our database. Severe headache and sudden loss of consciousness were the most common symptoms, reflecting the tendency of AVMs to bleed during initial diagnosis.

supratentorial and infratentorial lesions present with a slightly different pattern of symptoms. Curiously, some patients' brains adapt to the altered vascular environment and can remain asymptomatic, whereas some develop difficult symptoms owing to hemodynamic changes in the parenchyma.[31] Yet, the most common cause for diagnosis in both groups is still a hemorrhagic stroke (Figure 5).[9] AVMs used to mainly be diagnosed because of the rupture, but owing to changes in diagnostics, increasing numbers of AVMs are diagnosed unruptured.[2,53] Small AVMs tend to be diagnosed incidentally or when ruptured compared to larger AVMs.[54] This is partly because small AVMs do not become symptomatic as easily as the larger ones. AVM diagnosis is often verified with digital subtraction angiography (DSA) or magnetic resonance angiography (MRA), however, the first indication of a lesion can be noticed with the more conventional computed topography (CT) or magnetic resonance imaging (MRI).[31] DSA is needed before the treatment, as it provides the most accurate topography of the lesion. Figure 6 illustrates different imaging modalities from the same patient, diagnosed with a ruptured infratentorial AVM.

2.1.4.1 Epilepsy

An epileptic seizure is the second most common symptom leading to AVM diagnosis.[14] Of the patients who present with an epileptic seizure, on average 60% develop epilepsy within the next 5 years if untreated.[55] Epilepsy independently is also another factor associated with decreased quality of life (QoL).[56] Sometimes seizure-freedom can be met with resection of the AVM, however, drug-resistant epilepsy alone is rarely the only indication for surgery.[56] Having complete seizure-freedom has

Figure 6A (left): Preoperative CT image (axial-plane) showing a right-sided infratentorial ICH.

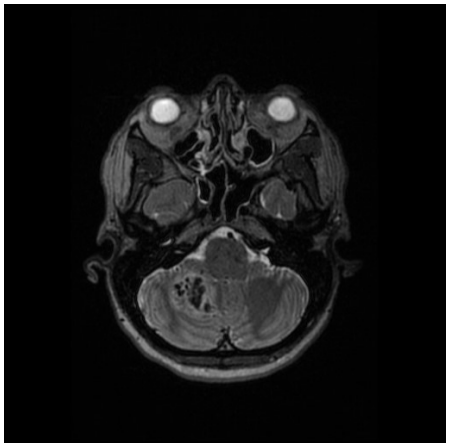

Figure 6A (right): Preoperative MRI image (axial-plane, T2 sequence) from the same patient. The cerebellar AVM is better visualized.

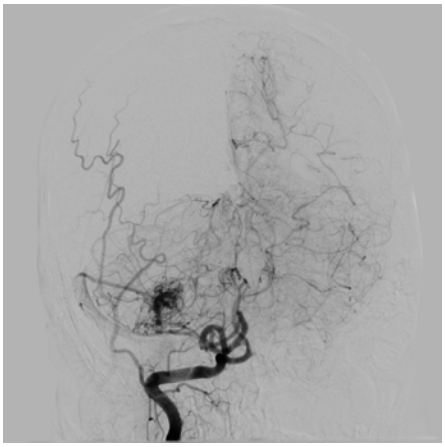

Figure 6B (left): Preoperative 3D rotational DSA (anterior-posterior view) of the patient in Figure 6A. An infratentorial, right-sided AVM draining to the adjacent sinus is presented.

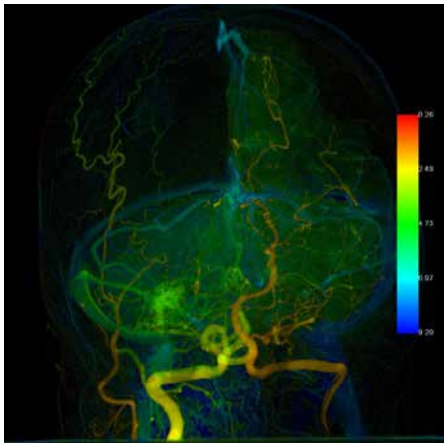

Figure 6B (right): Preoperative DSA, color-coded according to flow delay / transit time for the contrast agent. The premature drainage into the sinus on the AVM side can be distinguished by the green color of the right-sided transverse sinus, compared to the normal blue-colored sinus on the left-side.

been associated with improvement in social adjustment and occupational integration.[57] Despite being symptom-free most of the time, having epilepsy can reduce the person's QoL on many levels.[56] Examples of this are driving restrictions and social stigmas, which are both associated with the inability to continue a premorbid lifestyle.[56] Additionally, the psychological strain of the disease might independently decrease a person's everyday performance level.[58] In addition to this, the prevalence of patients with neurobehavioral disorders, such as

cognitive or behavioral disorders, is higher among patients with epilepsy, and these have shown connection to reduced HRQoL.[59]

2.1.5 Natural history

Natural history studies aim to investigate the natural course of the disease, the course from the pathological onset until either recovery or death. To make treatment decisions, clinicians and patients need to understand the natural course, because this is weighed against the risks related to treatment. The rarity of AVMs and the usual hemorrhagic presentation have complicated how AVM natural history studies are conducted because, with modern knowledge, patients presenting with a ruptured lesion are often treated, thus the real natural history is ended. However, there are some historical AVM patient-series with only minimal selection bias, from which AVM natural history estimates have been published.[45, 52, 60] In the following sections, I cover the risk of AVM hemorrhage and excess mortality first based on the Helsinki natural history series,[45, 52, 61] and later the series from other research groups.

2.1.5.1 Rupture risk in theory

The risk of AVM hemorrhage is highly dependent on multiple factors and depends on the time when the risk is assessed. Two different lesions can harbor a very different annual rupture risk depending on various characteristics. The theoretical risk is cumulative by nature. If we assume the annual risk of hemorrhage stays the same for one individual (what we actually know is not the case), then we can estimate the cumulative rupture risk c for the supposed lifetime with the formula $c = 100\% * (1 - (1 - p)^t)$, where p is the annual probability of hemorrhage and t is the time at risk in years.[62] The

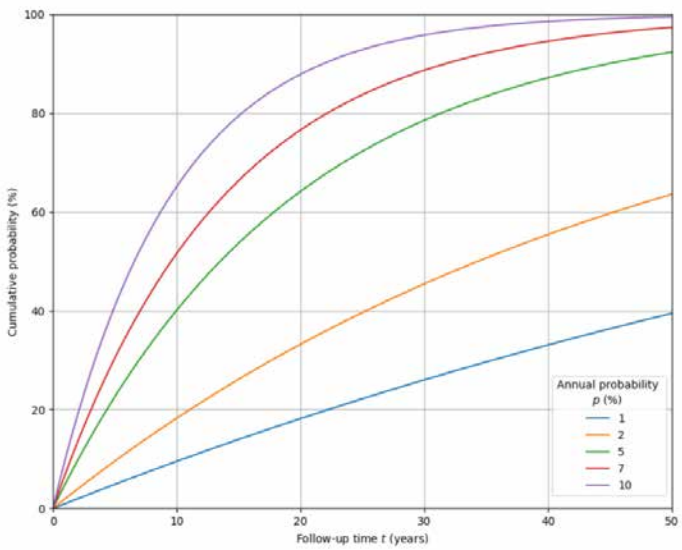

Figure 7. $c = 100\% * (1 - (1 - p)^t)$, cumulative rupture risk c for the supposed lifetime where p is the annual probability of hemorrhage and t is the time at risk in years. It is assumed that the theoretical annual rupture risk stays constant. The increase in cumulative probability/risk is highest during the first years after diagnosis also theoretically. Note: despite high cumulative probability on the purple curve, the theoretical risk will never reach 100%.

theoretical increase in the risk is the highest during the first years after the beginning of calculation, and the curve flattens as time progresses. Clinically, the cumulative nature means that for young AVM patients even if their yearly rupture risk was small, say 1–2%/year at diagnosis, because of the life-expectancy of several decades, the risk increases to a significant figure even before they retire. This theoretical nature of cumulative rupture risk is illustrated in Figure 7. What we know from the literature is that the annual rupture rate does seem to be the highest during the first years after diagnosis and decreases in follow-up. This phenomenon has been reported by many researchers.[45, 60, 63, 64] One reason behind this could be that the AVMs which become symptomatic might experience changes in the hemodynamics in the lesion and adjacent brain regions and this could be indicating a near-future rupture.

Finally, an often-confusing aspect in risk factor studies is the differing associations of risk factors for ''hemorrhagic presentation'' and for ''future hemorrhage''. For example, small AVM size has been associated with hemorrhagic presentation, however, large AVM size has been associated with future hemorrhage.[54, 65] This seems confusing but could at least partly be explained by the fact that small AVMs cause symptoms proportionally more seldom than large AVMs. This leads to the bias that small AVMs are more often diagnosed when ruptured (Figure 8), even though small size itself is not a true risk factor for AVM hemorrhage.[45] This ''over-presentation'' with hemorrhage can influence rupture risk studies and is an important factor to consider when conducting statistical tests, for example. The true risk factors for hemorrhage are discussed in the following section.

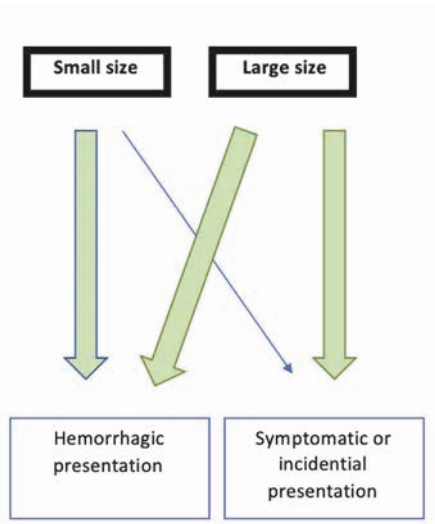

Figure 8. Schematic illustration about the phenomenon leading to small size often being associated with hemorrhagic presentation, even though it is not a true risk factor for rupture. Because small AVMs tend to cause symptoms proportionally less often than larger AVMs, it appears that they are associated with hemorrhagic presentation. Note: we do not know the exact number of undiagnosed AVMs, as some might remain asymptomatic for a whole lifetime. Supposedly, small AVMs remain asymptomatic more often than larger AVMs.

2.1.5.2 The Helsinki series

The Helsinki AVM database introduced in section 1.2 includes patients treated in the Department of Neurosurgery at HUH from 1942 onward. The department was the only neurosurgical department in Finland until the late 1960s. At the time the natural history studies were conducted, the catchment area of HUH was around 2 million citizens.[45] Owing to the Finnish public healthcare system, all Finnish AVM patients are treated in university hospitals. The data related to the patient and treatment are registered in electronic patient registries, which are easily accessible for retrospective data collection. Also, Finns are genetically a relatively homogenous population, which makes Finland an ideal country for epidemiological studies.

2.1.5.2.1 Risk factors for AVM hemorrhage

The Helsinki natural history series rupture risk study included 238 patients admitted between 1942 and 2005 with at least 1 month of hemorrhage- and treatment-free follow-up time (mean follow-up time of 13.5 years). During the 3222 person-years of follow-up, there were 77 hemorrhages, concluding an overall 2.4% rupture rate.[45] Demonstrating the phenomenon discussed earlier, the annual rupture rate was the highest during the first few years after the diagnosis, and for the whole patient cohort this meant a 4.7% annual rupture rate during the first 5 years after diagnosis and a 1.6% annual rate afterward, translating into the average 2.4% annual rupture risk during the whole follow-up time.[45] This is comparable to a meta-analysis of untreated brain AVMs in 2525 patients during 6074 patient-years of follow-up, in which the overall annual rate of hemorrhage was 2.3% (95% confidence interval (CI): 2.0–2.7) for the following 10 years after initial diagnosis.[66] There was an overall 21% (95% CI: 12–27%) 5-year rupture rate and a 39% (95% CI: 32–47%) 20-year rupture rate after admission.[45]

However, as mentioned, the risk varies between patients and depends on multiple factors, presented in Table 1. Similarly, as with the rupture rates the risk factors possess a different behavior in the statistical models according to the time period evaluated, meaning that for example a certain characteristic can increase the rupture risk in the first five years of follow-up but then not after. This is partly explained by the effect certain AVM features and patient characteristics have on the treatment decisions and outcome. For example, more easily treatable lesions can lead to exclusion from the cohort (=end of natural history) earlier than more difficult lesions, which are carefully observed rather than interventionally treated. Referring to the Helsinki natural history study, according to the multivariate proportional hazard models, the independent risk factors for rupture during the whole follow-up period (mean 13.5 years, range: 1 month to 53.1 years) were a previous rupture, large size (>5cm in diameter), and deep and infratentorial location (Table 1).[45] These factors are also supported by other natural history studies.[65-68] Another interesting finding (from Model 3, not illustrated in Table 1) was that the

combination of deep location and previous rupture increased the relative risk (RR) up to 4.21 (95% CI: 1.19–14.9).[45] Additionally, exclusively deep venous drainage was another significant risk factor increasing the rupture rate, however, only during the first 5 years after diagnosis. This increase in rupture rates was significant only in the univariate Kaplan–Meier curves, which demonstrated a 34% (95% CI: 20–48%) cumulative rupture rate during the first 5 years, compared to 20% (95% CI: 12–28%) for cortical drainage and 5% (95% CI=0–13%) for cortical and deep drainage.[45] From the univariate Kaplan–Meier curves, the largest increase in the rupture rates was with an infratentorial location during the first 5 years after diagnosis, when the

Table 1. RR5 = relative risk in the first 5 years after diagnosis, RRO = relative risk during the whole period. Models were created with Cox regression analyses, with the following differences: Model 1 included all the tested variables and did not include the interactions between the tested variables and excluded the non-significant variables using a stepwise procedure; Model 2 included all the variables without exclusion and calculated adjusted RRs for all of them; and Model 3 used the stepwise procedure and also included the interactions between the variables (except the interactions between age and sex). Model 3 did not produce significant risk factors for the first 5 years and is not therefore included in the RR5 column. The table is adapted from *Hernesniemi JA, Dashti R, Juvela S, Vaart K, Niemela M, Laakso A. Natural history of brain arteriovenous malformations: a long-term follow-up study of risk of hemorrhage in 238 patients. Neurosurgery. 2008;63(5):823-831.*

	RR5* (95%-CI)		**RRO (95%-CI)**		
	Model 1	Model 2	Model 1	Model 2	Model 3
Age per year	-	0.99 (0.97–1.02)	-	0.99 (0.97–1.01)	-
Male sex	-	0.66 (0.34–1.29)	-	0.76 (0.46–1.26)	-
Previous rupture	**2.44‡ (1.06–5.62)**	2.09 (0.86–5.05)	**2.23‡ (1.23–4.05)**	**2.02‡ (1.08–3.78)**	**2.63‡ (1.43–4.84)**
Location					
Infratentorial	-	2.68 (0.98–7.32)	**2.89‡ (1.30–6.43)**	**3.07‡ (1.37–6.87)**	**2.89‡ (1.43–4.84)**
Deep	**2.04‡ (1.04–3.99)**	2.57 (0.76–0.86)	**1.83‡ (1.08–3.10)**	2.10 (0.9–4.91)	-
AVM size					
Small	-	1.00	1.00	1.00	1.00
Medium	-	1.40 (0.6–3.27)	1.80 (0.98–3.32)	1.74 (0.93–3.27)	1.65 (0.9–3.05)
Large	-	**3.20‡ (1.26–8.14)**	**3.13‡ (1.55–6.30)**	**3.51‡ (1.73–7.15)**	**3.30‡ (1.63–6.66)**
Venous drainage					
Cortical and deep	-	1.00	-	1.00	
Cortical	-	4.92 (0.98–24.7)	-	2.04 (0.82–5.13)	
Deep	-	3.83 (0.78–18.8)	-	1.67 (0.67–4.15)	

‡ indicates statistical significance, 2-tailed p<0.05.

factor was associated with an 11.6% annual rupture rate, followed by deep location (8.9%) and deep venous drainage (8.1%). Other natural history studies have also recognized infratentorial location as a risk factor for hemorrhage, even though it does not always remain significant in the multivariate models.[64, 65] Finally, patients who experienced hemorrhage (29.3y±1.4y) were younger during admission than patients with no rupture (34.4y±15.1y).[45] However, controversy exists since increasing age has been found as a predictor of subsequent hemorrhage by others.[65] Results about hemorrhagic presentation are also contradicting, with some finding increasing age[66] and some younger age predictive.[69] Despite the lack of general agreement on the risk factors for hemorrhage, it is generally acknowledged that factors whose absence should protect the patient from rupture have been recognized.[70]

2.1.5.2.2 Excess mortality

The diagnosis of AVM is associated with a significant excess mortality in long-term follow-up compared with the general population of Finland.[61] This finding is from a natural history study of 623 Finnish AVM patients with a total of 10,165 person-years of follow-up. The mortality is highest during the first year after diagnosis and decreases slightly after but remains elevated in the long-term owing to its cumulative nature.[61] The increase in the first years after diagnosis is understandable, as this is the time when treatment- and hemorrhage-related mortality is highest.[61] However, even after 20 years AVM-related deaths constituted approximately half of the causes of death in the study cohort. Women experienced more AVM-related deaths compared to men (60% vs. 43%), who had a higher proportion of cardiovascular disease (11% vs. 20%) and trauma and other disease (11% vs. 25%) as a cause of death.[61] Mean age at an AVM-related death was 43.2 years (SD: ±17.9y). Men had also a higher excess mortality, even though there were no significant differences with respect to age, lesion characteristics, proportion of hemorrhagic presentation, treatment or length of follow-up compared to women. Compared to the general population, men experienced significant excess mortality with cumulative relative survival ratio (CRSR) of 0.89 (95% CI: 0.84–0.92) after 5 years, a CRSR of 0.70 (0.64–0.76) after 20 years and a CRSR of 0.58 (0.48–0.65) after 30 years, compared to women with CRSRs of 0.92 (0.88–0.95), 0.87 (0.79–0.94) and 0.85 (0.74–0.95), respectively. Surprisingly, AVM rupture during admission did not significantly increase the mortality compared to unruptured AVMs in the long-term, rather the effect of successful treatment was more meaningful in preventing excess mortality. Interestingly, partial occlusion also started showing a favorable effect after 5–7 years of follow-up compared to untreated AVMs.[61] Patients whose AVM was unruptured and totally occluded with treatment had the best outcome regarding excess mortality, with only 1.9% excess mortality during the first year after diagnosis (RSR 0.98, 95% CI: 0.92–1.00), and after the first year there were no statistically significant

differences in excess mortality compared to the general population.[61] Patients with ruptured AVMs that were totally occluded with treatment had 3.3% excess mortality during the first year, and a 10-year CRSR of 0.94 (95% CI: 0.89–0.97) and a 30-year CRSR of 0.90 (95% CI: 0.77–0.99). In comparison, the respective numbers for conservatively treated patients were CRSR 0.72 (0.63–0.79) and 0.49 (0.38–0.59).[61]

2.1.5.3 ARUBA and other series

A comparable figure to the Helsinki series yearly rupture rate was found in a meta-analysis of untreated brain AVMs in 2525 patients during 6074 patient-years of follow-up, in which the overall annual rate of hemorrhage was 2.3% (95% CI: 2.0–2.7) for the 10 years after initial diagnosis.[66] The rate was higher for ruptured AVMs (4.8%, 95% CI: 3.9–5.9%) compared to unruptured (1.3%, 95% CI: 1.0–1.7%) lesions at the initial presentation. The recently published findings from the ARUBA randomized controlled trial (discussed in section 2.1.6.7) reported a 2.3% crude annual rupture rate for previously unruptured and untreated AVMs.[71] The risk factors found to be significant by the existing natural history literature mainly consist of patient characteristics and anatomical features of the lesion.[68] The modifiable, classic cerebrovascular risk factors, such as smoking and hypertension, have not been directly associated with the risk of rupture in AVM patients, and are discussed more in detail in section 2.3.2. The most often reported predictors for AVM hemorrhage during follow-up include prior hemorrhage, larger diameter and deep or infratentorial location.[66, 67, 72] Predictors for hemorrhage in the initial presentation have only been reported in a few studies, in which two have reported similar risk factors of deep or infratentorial location and small diameter,[73, 74] however, opposite findings have been reported by one study.[75] The annual mortality rates for AVM patients range from 0.7 to 2.9%, however, reports taking into account the background population mortality are scarce.[13, 63, 76-79] Hemorrhagic presentation was associated with increased mortality in the study by ApSimon et al., however, neither Ondra et al. nor Crawford et al. found any difference in the mortality between hemorrhagic and non-hemorrhagic presentation.[13, 76, 77] In the ARUBA trial 50.4-month follow-up, there were 6 deaths total in the whole study cohort, with no statistically significant difference between the medical management and interventional therapy groups.[71]

2.1.6 Management

2.1.6.1 Current conservative management

For some patients the risks related to interventional treatment exceed the risk of rupture. In practice, these are patients either with a difficult-to-treat lesion or those whose cumulative rupture risk is not high, usually owing to old age during diagnosis. Furthermore, some patients do not wish to be treated with interventional methods, despite clinical

meaningfulness. In these cases, the current medical treatment is based on the symptoms of the patient and careful follow-up. As discussed earlier, of the patients who are diagnosed with an epileptic seizure caused by AVM 60% develop epilepsy within the following 5 years.[55] Antiepileptic drugs (AED) used in seizure-control vary between patients depending on the adverse effects, patient characteristics and preferences. Chronic headaches are a common complaint with AVM patients and create a meaningful goal for conservative management.[6] ARUBA (discussed in section 2.1.6.7) did not find any difference in the outcomes for headache in their comparison of interventional therapy and medical management, although this was not a primary end-point in their study.[53] There are no studies assessing the usefulness of medication in the treatment of AVM-associated headache.[80] In the more acute scenario after AVM rupture, the cardiorespiratory situation as well as other systemic responses need to be treated. These include treatment of systemic hypertension, fever, hyperglycemia and intracranial hypertension, and deep vein thrombosis prophylaxis.[81] An important part of the conservative treatment is also the monitoring in the intensive care unit, which allows quick responses to the changes in a patient's condition in acute scenarios.

2.1.6.2 Introduction to interventional therapy

As in all interventional treatment modalities, there are several major treatment-related risks. These risks need to be carefully weighed against the risks of hemorrhage and its consequences. The panel of the European consensus conference on unruptured brain AVMs concluded that treatment complications may overcome the risk of hemorrhage, however, with young patients the risk of complications from treatment are far more minor than the risk of rupture with low-grade AVMs.[70] In contrast, the panel regarded a life expectancy of minimum 20 years as a precondition for interventional treatment, meaning that patients with unruptured AVMs aged over 65 years should preferably be treated conservatively.[70] Other factors that need to be considered when planning the treatment are first the clinical presentation of the patient (symptomalogy, cumulative rupture risk, patient's opinion), second the anatomical features of the AVM, third the institutional preferences and policies, and finally the expertise and availability of the personnel performing the interventional modality of choice.[82] Especially with lesions that have already ruptured, it is advisable to go into interventional management more eagerly, since previous rupture notably increases the risk for subsequent hemorrhage.[83]

The goal of AVM treatment is a total occlusion of the lesion, as even the smallest residuals pose a significant risk of hemorrhage.[52] Occasionally, treatment can be indicated to achieve control of epileptic seizures or to stop progressive neurological symptoms from developing.[5] AVMs can be treated with microneurosurgery, endovascular embolization, stereotactic radiosurgery (SRS) or a combination of

these. Microsurgical resection is often regarded as the gold standard for Spetzler-Martin grade (SMG) I and II AVMs.[54] SRS can also be used as a primary method for AVM occlusion or after endovascular embolization.[84] Finally, embolization is most often used as an adjunct either before microsurgery or SRS, however, for carefully selected cases it can also serve as a primary treatment modality.[84] Surgical resection is often more efficient than the endovascular methods, which might need multiple treatments before the lesion is completely eradicated.[54, 85] However, microsurgery requires an open cranial surgery, which usually takes longer to recover compared to embolization.[54] SRS can be needed in the treatment plans of the more complicated AVMs.[86] A problem with SRS is possible ineffectiveness, as it might take up to three years to reach total obliteration.[53] Furthermore, the desired treatment effect might not be reached at all, despite sacrificing the adjacent parenchyma to radiation edema or even necrosis.[6] However, the risks related to SRS on eloquent or deep areas of the brain are considered minor to the risks associated with microsurgery, and therefore it is sometimes the preferred modality with small unruptured AVMs.[70] Also, for large, inoperable AVMs, staged radiosurgery might be the method of choice if lesion eradication is deemed necessary.[70]

2.1.6.3 Microsurgical treatment

AVM surgeries create one of the most difficult fields of neurosurgery, and therefore should be directed only to specialized institutions.[87] What makes AVMs difficult to operate on is not only the nature and variety of the lesions, but also the rarity. Everything begins before the operation itself with careful planning and a review of the available images. From the angiographic images, the feeding arteries, the territories feeding the nidus, the transit arteries, the deep white matter feeders, the perforating arteries' involvement, the diffuseness of the nidus, the intranidal and extranidal aneurysms and the nature of venous drainage are evaluated. From MRI and CT images, the size and relationship of the nidus to the adjacent parenchyma and the surface of the brain can be evaluated, as well as the type of a possible associated intracranial hemorrhage. The positioning of the patient during the surgery needs to be carefully planned in relation to the craniotomy, the approach into the lesion and the general principles related to, for example, hemodynamics. Modern operating microscopes are of the greatest importance.[88] Otherwise, the operations can vary significantly between patients, and the following steps introduced here are only to provide a general picture of AVM surgeries.

The operation itself begins with the appropriate craniotomy, after which the dura is inspected for adherents to the dura.[88] After dural opening, the feeding arteries, the venous outflow and the transit arteries are located, with the help of indocyanine green videoangiography (ICG) if needed (Figure 9). The resection generally begins from the arterial side and progresses toward the venous side, therefore it is essential to distinguish the veins from the arteries before beginning occlusion.[88] An intraoperative AVM

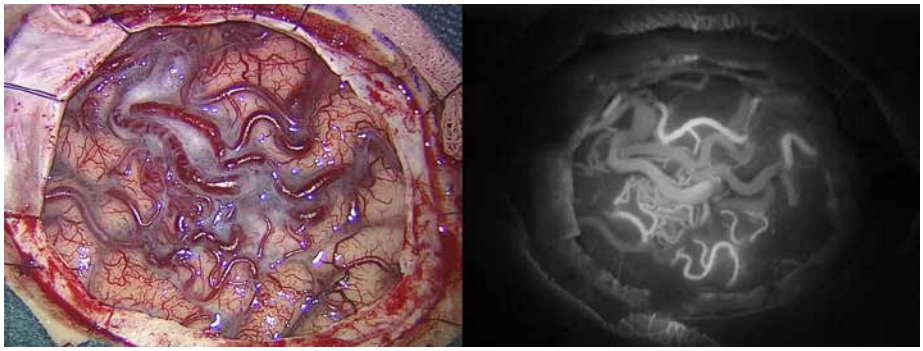

Figure 9. Intraoperative view of a cortical AVM, after craniotomy and dural opening (left). Intraoperative ICG videoangiography can be used to understand the flow of the AVM, to distinguish the feeding arteries from the arterialized veins (right).

hemorrhage can result from a premature occlusion of the draining veins and this might lead to catastrophic consequences.[88] In particular, the main draining vein should be preserved and carefully handled.[12] The coagulated vessels are then cut carefully while inspecting the possible signs of bleeding owing to inadequate coagulation. The small feeder arteries are the most difficult to coagulate, as the vessels do not have enough arterial wall for effective coagulation.[12] Bleeding from these vessels can turn the surgery into a catastrophe if not controlled promptly. Small clips can be used to try control the bleeding, but the technique used more often in our clinic is the so-called dirty coagulation.[88] Basically, the idea is to coagulate a small portion of the surrounding gliotic tissue with the vessel. Temporary clipping may be especially useful if it is still uncertain whether some particular vessel is a true feeder, an *en passage* artery that needs to be preserved, or even an arterialized draining vein that should not be coagulated at too early a stage (Figures 10 and 11). The final step in the removal is the coagulation and cutting of the last draining vein, which should at this stage be dark owing to the lack of arterial blood flowing through the nidus from the arterial side. Again, ICG can be used in the evaluation of the possible remaining feeders, since in the case of no remaining feeders the remaining vein should only fill in a retrograde fashion. After the final coagulation and cut, the nidus can be removed and the remaining area is carefully inspected to detect the remaining vessels, which could cause a hemorrhage if not coagulated. Finally before the closure, the surface of the resection cavity is coated with fibrin glue and Surgicel.[52]

In a literature review by Bradáč and Beneš comprising of 4296 patients in 32 surgical series, the mean efficacy (complete obliteration of AVM) was 96.9% (95% CI: 95.7–97.9%).[12] In the same review, the mean complication rate was 7.1% (95% CI: 5.6–8.8%), ranging from 1.2% to 21%. The complication rate increases as the anatomy becomes more complex.[89-91] Eloquence, in particular, is regarded as a problematic anatomical feature.[70] Therefore, it is sometimes advisable with eloquently located lesions to choose radiosurgery over microsurgery or endovascular treatment.[70]

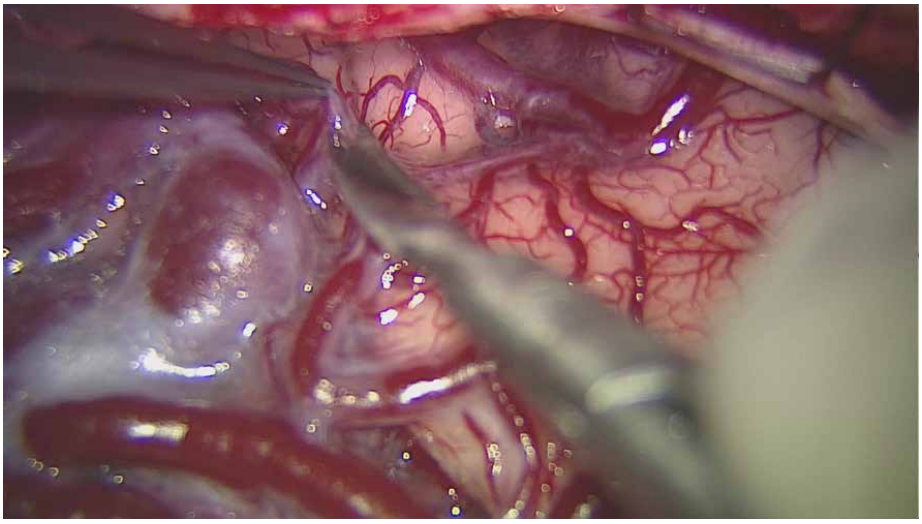

Figure 10. Arterial feeders on the perimeter of the nidus are sharply dissected free for coagulation or clipping.

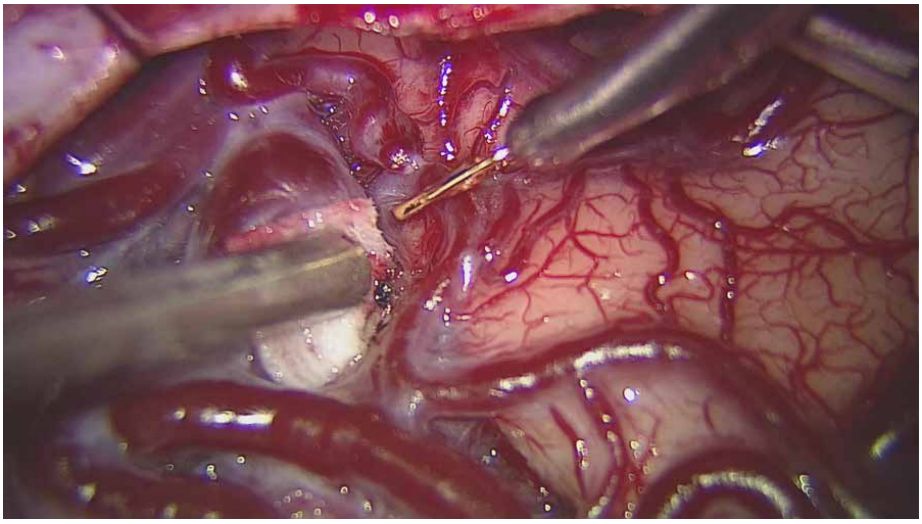

Figure 11. Applying a temporary clip on an arterial feeder. Clips are usually removed at a later stage and the artery coagulated with bipolar cautery and then divided.

2.1.6.4 Stereotactic radiosurgery and therapy

In SRS, radiation is focused to AVM by using a variety of instruments and techniques over a single session. If multiple sessions are needed, for instance if the radiation dose needs to be fractioned because of proximity of a vital structure, the intervention is called stereotactic radiotherapy (SRT). SRS and SRT can be provided with different equipment and sources of radiation: the Gamma Knife©, linear accelerators and proton beam radiosurgery, and, despite the names, these methods are non-surgical.[6] The mechanism of action

remains incompletely understood, however, according to current knowledge the radiation induces a destruction of the endothelium and a proliferation of myofibroblasts, which help occlude the lesion.[92] Owing to these mechanisms, achieving a total occlusion usually takes 2–3 years, during which the risk of hemorrhage is still significant.[93] SRS and SRT are regarded effective for AVMs smaller than 3.5cm in diameter.[6] In a literature review of 9489 patients from 45 studies, the mean efficacy of these methods were 64.2% (95% CI: 59.4–68.9%), ranging from 35–92%.[12] Factors associated with better obliteration rates include small AVM size, non-eloquent location and low-flow pattern.[94] Understandably, radiation can induce adverse effects to the surrounding tissues, which increases the complication rates of this modality. These complications include blood–brain barrier breakdown, necrosis, edema and cyst formation.[92] Roughly 10% of patients get symptomatic adverse changes, however, the risk is associated with the location of the AVM, target volume and margin dose (surrounding normal tissue dose).[84] These adverse effects can be treated to some extent with corticosteroids, and in some cases with bevacizumab.[95] However, 2–3% of patients experience permanent neurological changes from adverse effects.[96]

2.1.6.5 Endovascular treatment

In endovascular embolization the feeder arteries and the draining veins are occluded using liquid endovascular agents, such as n-butyl-2-cyanoacrylates, or more frequently Onyx®, which is ethylene vinyl alcohol copolymer dissolved in a potent organic solvent dimethyl sulfoxide. These are guided into the AVM using guiding catheters and microcatheters. Onyx is not a glue like the cyanoacrylates, therefore it does not have the same problems of adherence of the microcathethers.[97] In addition to liquid embolisates, platinum flow coils can be used in occlusion.[12] The standard method is to access the AVM transarterially, however, transvenous methods also exist as an option. In addition to the liquid embolisates, detachable coils can also be used to occlude large arterial feeders.[84] Embolization is most often used as an adjunct to microsurgery or SRS to occlude or reduce the feeders of a large AVM, however, there are considerable differences in institutional preferences.[12, 45] Preoperative embolization is covered in section 2.1.6.7 about multimodal therapies.

As with all the interventional methods, embolization possesses its own risks of complications, most notably hemorrhagic complications either intracranially or during the navigation.[98, 99] In a literature review by Bradáč and Beneš comprising 4787 endovascularly treated AVM patients from 33 series (larger than 30 patients) the mean efficacy was 29.6% (95% CI: 22.6–37.2%), meaning that 29.6% of patients treated with Onyx received total occlusion of the lesion.[12] However, for highly selected patient series of simple-featured AVMs, the obliteration rate can be as high as 96%.[100] Regarding complications, the same review concluded that the more aggressive the attempt to completely occlude the

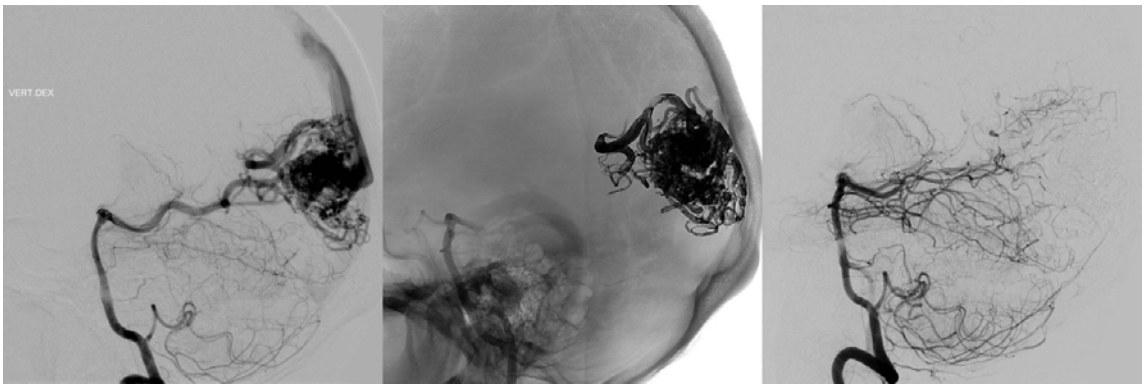

Figure 12. DSA illustrating contrast agent filling the AVM before embolization (left). The AVM is embolized with Onyx, which is visible in a traditional X-ray image (middle). Postembolization DSA shows complete lesion occlusion, the radiocontrasting agent is similarly subtracted as the surrounding skull (right).

lesion, the larger the complication rate, with the mean of 7.4% (95% CI: 6.3–8.5%), ranging from 2% to 17%.[12] The most common complications are ICH and ischemic stroke (IS).[101] Recurrent AVMs, verified with DSA, have been reported even after a total obliteration with embolization.[102-105] In a literature review by Potts et al. consisting of 32 studies with 3624 patients, however, of the 668 patients with a reported total obliteration, only 4.5% had a reported recurrent AVM in a follow-up angiography.[106] Based on their results, they concluded that embolization can provide a permanent cure, but follow-up angiographies are still justified. Reasonable explanations for the recurrence include recanalization through the embolized vessel, revascularization, and as a biasing factor an incomplete embolization in the initial phase, owing to poor visualization to all the compartments of the nidus.[107] Notably, curative embolization often requires multiple treatments, and often a total obliteration cannot be met despite efforts.[104, 108] In rare cases, embolization can be used in a palliative manner to reduce symptoms owing to the vascular steal phenomenon caused by the AVM or to treat AVM-related high-risk lesions, such as associated aneurysms or arteriovenous fistulae.[84]

2.1.6.6 Multimodal strategies

Embolization (introduced above) can be used before microsurgery to aid in the resection. Deep feeders, which are generally considered problematic for microsurgical resection, can be selectively embolized before operation, although this approach poses its own treatment-related risks.[70] There is no consensus about the timing of embolization in relation to surgery, as no evidence supporting either an immediate or delayed presurgical approach exists.[84] However, our institutional preference favors surgery the same or next day to avoid embolization-induced ruptures. Targeted embolization can also be used presurgically to occlude AVM-related aneurysms or a venous ectasia.[12] Before

SRS, embolization is commonly used with AVMs larger than 3cm in diameter.[84] The goal of this strategy is to reduce the size of AVM to optimize the effectiveness of SRS. Also, certain high-risk features can be treated endovascularly to reduce the rupture risk during the latency period of SRS.[109] This is a rather new method, and there is not enough research evidence to support it yet.[84] In addition, if the total obliteration of a large AVM cannot be met with staged SRS, it can be followed by surgery or endovascular treatment.[70]

2.1.6.7 ARUBA

ARUBA, a randomized controlled trial of unruptured brain arteriovenous malformations, has sparked a lot of debate about the treatment recommendations of AVMs.[53] The trial was designed to compare interventional therapy (microsurgery, SRS, embolization) to medical therapy (i.e., conservative treatment for unruptured AVMs). The original trial was published in the *Lancet* with 226 patients with a 33-month follow-up with the conclusion that the risk ratio for the primary end-point (death or a symptomatic AVM hemorrhage) in the medical-arm was 0.27 (95% CI: 0.14–0.54) compared to the interventional arm.[53] Recently, the ARUBA investigators published their long-term outcomes, namely after a mean 50.4 months (standard deviation (SD) =22.9 months) of follow-up, with similar conclusions that medical management should be preferred over interventional treatment in patients with unruptured brain AVM.[71] Owing to some issues in the trial design and protocol, many have considered its results as not generalizable to all unruptured AVMs or to all interventional modalities.[70] Altogether 1740 AVM patients were screened for the trial, however, 87% had to be excluded from the final cohort owing to various reasons: 323 patients did not want to participate, in 177 cases the clinicians did not follow the study protocol and 1014 patients were excluded because they had had a previous intervention or hemorrhage from the AVM.[53] Additionally, despite the interventional treatment arm having more than two-thirds of the patients with SMG I and II AVMs, only 5 patients in the arm were treated with microsurgery as monotherapy, compared to 80% of the patients with SRS and/or embolization. This proves especially problematic, as microsurgery is regarded as the golden standard for unruptured SMG I and II AVMs.[110] Even with the extended follow-up time, the occlusion rate of AVMs in the interventional group was a mere 44%, illustrating these rather suboptimal treatment strategies in the interventional arm.[71] This shortcoming in the outcome is reflected in the high event rate in the therapeutic group, which was almost 50% higher than what was expected in their statistical power analysis and when compared to existing literature.[110] What re-occurred in their most recent publication was that the outcome rates in the interventional group were noted to be comparable to a meta-analysis by van Beijnum et al.[6] For reference, this meta-analysis reports death/symptomatic stroke rates of 7.4% (range 0–40%) after microsurgery, 6.6% (range 0–28%) after embolization and 5.1% (range 0–21%)

after SRS for unruptured lesions, whereas the comparable figures in ARUBA were 29% (1.5–54%), 25% (7.6–55%) and 13% (0–63%), respectively.[6, 53]

2.1.7 AVM classifications

2.1.7.1 Spetzler–Martin grading system

The SMG was introduced by Drs. Spetzler and Martin in 1986.[111] In the grading system, patients are classified from 1 to 5 depending on the anatomical features of their AVM.[111] SMG is a surgical scale assisting in the decision-making of the treatment modality.[87] It is commonly used in neurosurgical research.[87] Table 2 introduces the criteria used in SMG classification. Lesions are graded based on three categories: size of the nidus (1–3 points), eloquence (0–1 point) and venous drainage (0–1 point), leading to a minimum of 1 point and maximum of 5. The number of points leads to a respective SMG class.

2.1.7.2 Spetzler–Ponce grading system

The original SMG was converted to the 3-tier Spetzler-Ponce (SPC) in 2011, owing to similarities in the far-ends of the spectrum of the SMG (Table 2).[87] From the studies using functional outcome instruments, such as modified Rankin Scale (mRS), it has been determined that the SPC A lesions are most often suitable for surgical management.[5, 50, 112] SPC B lesions create the trickiest group with regard to decision-making, falling between the SPC A lesions and the

Table 2. Spetzler–Martin grade (SMG) deduction and translation into Spetzler-Ponce grade (SPC). *Eloquent location determined as brainstem, thalamus, hypothalamus, cerebellar peduncles, or sensorimotor, language or primary visual cortex.

Points for SMG, one set of points from each category: Size of the nidus; Eloquence; Venous drainage.				
	Points		Points from all three categories summed	
Size of the nidus			SMG 1 1 point altogether	SPC A
Small	1	1–3 points		
Medium	2		SMG 2 2 points altogether	
Large	3			
Eloquence*			SMG 3 3 points altogether	SPC B
Non-eloquent	0	0–1 point		
Eloquent	1		SMG 4 4 points altogether	SPC C
Venous drainage				
Superficial	0	0–1 point	SMG 5 5 points altogether	
Deep	1			
Total	1-5			

difficult SPC C lesions. One part of this trickiness is the phenomenon that to fall into the SPC B category (=SMG 3) you can have many various combinations of the anatomical variables. This leads to this group being rather heterogenous compared to the SPC A and SPC C groups.[113] The treatment of SPC B patients has created a lot of debate on the microsurgical field. To this question we aimed to provide new insight with our long-term HRQoL data on AVM patients.

2.1.7.3 Lawton–Young grading scheme

A supplementary grade was developed to be used in addition to the SMG, to improve the accuracy of the evaluation of treatment outcome in patients with brain AVM.[114] The grade takes into account a patient's age, the hemorrhagic presentation and the nidus compactness (Table 3). It has been validated with multicenter studies and has shown better accuracy in predictions than SMG alone, especially with cerebellar AVMs.[115-117]

Table 3. The Lawton–Young grading system. Patients can receive up to 5 additional points which illustrate the difficulty of surgery.

Age	
<20 years	1 point
20-40 years	2 points
>40 years	3 points
Hemorrhagic presentation	
Yes	1 point
No	0 points
Nidus diffuseness	
Diffuse	1 point
Compact	0 points

2.2 Outcomes of patients with brain arteriovenous malformation

In a systematic review and meta-analysis of AVM treatment comprising 142 study cohorts and 13,698 patients with 46,314 patient-years of follow-up, van Beijnum et al. compared the outcomes after each treatment modality.[6] Overall, male sex, younger age, SMG I–III AVM, small AVM size and exclusively deep venous drainage were associated with a lower case fatality. Table 4 compares the findings for each modality (as a primary modality only). SRS had the lowest case fatality; however, the hemorrhage rates were high after SRS and embolization. Microsurgery had low hemorrhage rates in follow-up and a high proportion of patients who received a total obliteration of the AVM.[6] These patient cohorts represent selected AVM patients, since they are collected from observational studies. To date, there is no randomized controlled trial (RCT) comparing interventional AVM treatment modalities against each other.

2.2.1 Surgically treated patients

For the low-grade AVMs (SPC A), surgery is often regarded as the gold standard. In a summary of 12 studies consisting of 1235 surgically treated patients with unruptured low-grade AVM, the mean postoperative morbidity was 2.2% (range 0–6.6%), and mortality 0.3% (0–2.2%).[118] After ICH, the mortality rate for ruptured AVMs is understandably higher, numbers as high as 67% have

Table 4. van Beijnum J, van der Worp HB, Buis DR, et al. Treatment of Brain Arteriovenous Malformations: A Systematic Review and Meta-analysis. JAMA. 2011;306(18):2011–2019. doi:10.1001/jama.2011.1632

	Case-fatality*	Hemorrhage rate*	Complications‡	Obliteration⁰
Microsurgery	0.68 (0.61-0.76)	0.18 (0.10-0.30)	7.4% (0-40%)	96% (0-100%)
SRS	0.50 (0.43-0.58)	1.7 (1.5-1.8)	5.1% (0-21%)	38% (0-75%)
Embolization	0.96 (0.67-1.4)	1.7 (1.3-2.3)	6.6% (0-18%)	13% (0-94%)
Overall	0.68 (0.61-0.76)	1.4 (1.3-1.5)	-	-

*per 100 person-years (95% CI), ‡ leading to permanent neurological deficits or death, median (range), ⁰ median (range)

been reported,[60] however, these figures arise mostly from the historical patient series. With modern medical technology, the numbers from high-volume centers are around 12% to 20%.[3, 51] In Table 5, the surgical patient series published in the 2010s reporting the functional outcomes measured with mRS are collected. The factors associated with a better functional outcome postoperatively are younger age,[118] unruptured presentation,[50, 118] small AVM size,[50, 119] non-eloquent location,[119] cortical venous drainage,[119] SPC A lesion type,[50, 119] and good preoperative mRS.[118]

However, compared to the other causes of ICH, AVM patients have a lower odds of death (odds ratio (OR) =0.5, 95% CI: 0.4–0.7) and a better odds of favorable discharge from the hospital (OR=2.0, 95% CI: 1.4–3.0).[51] The better outcomes among ICH patients have been hypothesized to result from the AVM possibly bleeding into the nidus itself, or to the venous side and therefore sparing the healthy brain surrounding the lesion. Eloquent location is one of the factors associated with a worse outcome after a microsurgical obliteration of AVM. In particular, a sensorimotor or a language eloquence have been associated with poor outcomes.[123]

2.2.2 SRS and SRT patient series

SRS and SRT are typically chosen as the treatment modalities for patients whose AVM seems too risky for microsurgical resection.[70] These risky features include deep or eloquent location of lesion, large size and various patient-related factors (e.g., if the induction of general anesthesia is too risky). These differences in the background characteristics of the patients understandably are related to the outcomes of SRS, compared to patients treated with other modalities.[84, 96] Predictive factors for a successful outcome (complete obliteration of the lesion after the latency period) are AVM size (OR=0.88, 95% CI: 0.81–0.96), non-eloquent location (OR=3.2, 95% CI: 1.29–7.93), absence of perinidal angiogenesis (OR=2.61, 95% CI: 1.21–5.64) and low-flow pattern (OR=3.47, 95% CI: 1.6–7.53).[94] Several different SRS and SRT outcome scales have been developed to assess outcomes with regard to both obliteration and the functional outcome of the patient, and partly owing to this there is a shortage of pure mRS outcome studies reported among SRS patients.[124] However, these radiosurgical scores have shown associations to

Table 5. Microsurgical series of patients with brain AVM. Favorable mRS dichotomized classes are reported in the mRS column, followed with the percentage of patients with favorable mRS at follow-up, and number of patients in the whole study population.

Authors	Follow-up time, mean	AVM characteristics	Favorable mRS	% favorable	N (total)
Potts et al.[118]	1.8 years	SPC A unruptured	0-1	91	112
	1.6 years	SPC A ruptured	0-1	70	120
Javadpour et al[85]	6 months	71% SPC A unruptured	0-1	94	45
Schramm et al[50]	5.3 years	40% SMG II,30% SMG III, 50% ruptured	0-1	89.6	288
Morgan et al[119]	1.0 years	SPC A	0-1	98.1	359
	1.0 years	SPC B	0-1	77.8	203
Tong et al[120]	6.4 years	Cerebellar AVMs, 95% ruptured	0-2	89.5	181
Pohjola et al[121]	9.7 years	Ruptured infratentorial AVMs	0-2	66.6	36
Madhugiri et al[122]	4.0 years	Brainstem AVMs, 92% ruptured	0-2	51	39

mRS scores, although they are not completely interchangeable.[125] In a massive multi-center study of 2236 AVM patients (mean age 36.0 years, SD=±16.5y) undergoing Gamma Knife SRS with a mean 7 years of follow-up and average obliteration rate of 64.7%, the combined radiosurgical outcome was favorable (obliteration without post-SRS hemorrhage or permanent SRS-related symptoms) in 60.3% of the patients.[126] Predictors for poor outcome were high nidal volume, prior AVM hemorrhage, prior embolization, eloquent location, high number of isocenters and lower margin dose. In their analysis, there were radiation-induced imaging changes, which were symptomatic, in 9.4% of the patients, and the risk for developing these was increased in patients who received a margin dose greater than 24Gy.[126]

2.2.3 Endovascular patient series

The introduction of Onyx has improved the endovascular outcomes. Still, only a few patient-series with patients with fully occluded lesions exist, illustrating the rather adjunctive role of embolization in the modern treatment AVMs aiming for ''curative'' treatment.[54, 113] This is strengthened by the finding that a higher complication rate from treatment is associated with the aggressiveness of the endovascular treatment.[127] Hence, pre-surgical embolization not aiming for a curative treatment can be lower in the complication rates compared to embolization aiming for a total lesion occlusion.[128] This periprocedural complication rate is in relation to the anatomic characteristics of the lesion, since SMG V lesions might harbor a 25% complication rate, whereas for SMG II lesions the number can be five times

lower.[129] Other factors associated with an impaired functional outcome (mRS>0) include the presence of intranidal aneurysms, increasing age, and a deep venous drainage.[108, 127] There are very few purely endovascular outcome studies of AVM patients, mostly because of the treatment policies, which usually include other modalities owing to the inefficiency of embolization to totally occlude AVMs. However, embolization can yield favorable results if the patients are carefully selected, preferably in a multidisciplinary meeting.[70] However, the results from the few studies including patients treated with embolization only illustrate that the results are not as favorable as in the analogous surgical series: a study by Iosif et al. with a patient-series from their high-volume endovascular center, which included 73 patients with fully occluded SMG I–II lesions, the outcomes at 6 months follow-up were mRS 0 for 42.4%, mRS 1 for 21.9% and mRS 2 for 26.0% of the patients.[130] Owing to their decision of a dichotomization cut-point (mRS 0–2 = favorable), they reported that 90.5% of the patients received a favorable outcome and concluded that endovascular methods offer good clinical outcomes.[130] The lack of a purely endovascular series was recently discussed in a meta-analysis in which, out of the 1605 endovascular articles published, only 15 met the inclusion criteria for a purely endovascular series.[99] These 15 studies comprised of 597 patients with intent-to-cure embolization. The treatment goal (total obliteration) was achieved in 58.3% of the patients with an overall complication rate of 24.1%. The lesions were SMG I–III in 70.9% of the cases, with 34% of SMG III AVMs.[99]

2.2.4 Multimodal treatment patient series

In a recent retrospective analysis of 258 SPC A patients (48% presented with hemorrhage) treated with pre-operative embolization, the authors reported mRS <2 outcomes for 92.5% of the patients with unruptured AVM, and 88.0% for those with ruptured AVMs after a mean of 4.5 years follow-up.[131] Irreversible neurological morbidity in this study occurred in 1.2% of the patients.[131] An older study by Hartmann et al. with 119 patients with mostly medium- or high-grade lesions treated with endovascular embolization followed with microsurgical extirpation concluded that an increased treatment risk was associated with the combined therapy of endovascular therapy and microneurosurgery in the previously unruptured AVMs of their series.[132] Of these 35% of patients who presented with hemorrhage, 8% had SMG I, 27% SMG II, 40% SMG III and 22% SMG IV lesions. The factors associated with worsened long-term outcome were a deep venous drainage (OR 3.24, 95% CI: 1.35–7.80), an eloquent location (OR 2.42, 95% CI: 1.02–5.73), initial presentation with hemorrhage (OR 0.27, 95% CI: 0.11–0.69) and the maximum AVM diameter (OR 1.05, 95% CI: 1.01–1.09, per millimeter increase in size).[132]

2.2.5 HRQoL outcomes

Before our HRQoL study,[1] only a few papers on the QoL of AVM patients had been published.[56, 133-136] These had either been targeted at patients treated with radiosurgery pediatric patients, or had been rather small in sample size. The first one of these, published in 2002, discussed the impact of Gamma knife treatment before the total AVM obliteration on the QoL of 39 adult AVM patients.[135] Their conclusion was that the experience of hemorrhage did not significantly affect the perceived QoL, probably owing to the ''fear of the unknown'' in the non-hemorrhagic group, whose QoL was decreased.[135] Another RT QoL series published in 2012 with 78 AVM patients who had presented with seizure concluded that seizure freedom was significantly associated with an improved QoL and attaining employment after mean 7.6 years follow-up.[133] The largest impairments in QoL were perceived in the emotional domain (''Do you feel happy about your life?'') and the lowest in the familial domain (''Are you satisfied with your role as a family member or your family member's support?'').[133] In 2016, the first and so far only paper about QoL in pediatric AVM patients reported that in 26 patients with the mean age at diagnosis of 12.5 years and 6.8 year average follow-up period, factors associated with an improved QoL were a special education, corrective devices and functional status.[134] In 2017, the first microsurgical series on adult AVM patients' HRQoL was published.[56] Their study was limited by the small number of only 25 microsurgically treated patients. They discovered that the QoL of AVM patients was not significantly different from the age-matched values from the general population, and that patients with the main symptom of headache at diagnosis had impaired HRQoL compared to other causes.[56] Finally, in 2018, another QoL study with adult AVM patients was published, with the main intention to compare surgery to conservative management of unruptured AVMs.[136] The study included patient cohorts from Scotland and Australia, which were independently analyzed. Neither study population showed a significant difference in the HRQoL at 12 months between surgically or conservatively treated patients.[136]

2.3 Cerebrovascular risk factors

The discovery of high diastolic blood pressure as an IS risk factor dates back to 1967 and it sparked research into other cerebrovascular stroke risk factors.[137] Nowadays, it is estimated that as much as 90% of ISes or primary intracerebral hemorrhages (PICH) can be explained by the modifiable risk factors of high blood pressure, smoking, obesity, physical inactivity, poor diet, diabetes, extensive alcohol consumption, heart diseases, dyslipidemias and mental distress.[138-140] Cigarette smoking is regarded as one of the strongest etiological risk factors for stroke.[139, 142-145] Independently, it can more than double the risk of stroke.[146, 147] These findings have naturally

sparked the etiological studies of other types of hemorrhagic strokes, and smoking has been established as having a key role in the risk profile of these diseases as well.[148-151] A recent case–control study with Finnish twins was able to strongly connect cigarette smoking to fatal SAH, sealing its role as the most dangerous environmental risk factor of SAH patients.[152, 153] In their study, they also found a trend toward the other commonly reported risk factors, however, these findings were nonsignificant. Additionally, they reported that alcohol consumption was independently associated with fatal SAH, however, not after adjusting for smoking,[152] delineating the connection between notorious lifestyle habits. In the following section I review the known risk factors in non-traumatic hemorrhagic stroke.

2.3.1 SAH risk factors

Non-traumatic SAHs are caused by ruptured intracranial aneurysms (IA) in roughly 80% of the cases.[154] The lesions are roughly ten times more prevalent than AVMs, however, most IAs remain unruptured and unnoticed for the whole lifetime.[155] IA patients are on average 10–20 years older during diagnosis compared to AVM patients, and there is a female predominance.[156,157] Similarly, as in AVMs, most IAs present with hemorrhage.[154] This complicates the determination of risk factors, as we cannot ascertain the point of time when the patient has developed the lesion. Therefore, risk factor analyses of etiology and rupture have some understandable overlapping. When looking at SAH, the most well-recognized risk factors are smoking and hypertension (Table 6). These have

Table 6. Population-based case–control studies of males and females about the risk factors for SAH.

			Modifiable risk factors found significant by the study.						
	No of SAH	Population	SM	HT	AL	OC	TC	DM	BMI
Anderson[151]	432	ANZ	X	X	X			X	
Bonita[163]	115	New Zealand	X	X					
Fogelholm[149]	114	Finland	X						
Hannaford[164]	73	UK				X			
Isaksen[165]	26	Norway	X						
Kissela[166]	107	USA	X	X	X			X	
Lindbohm[153]	543	Finland							
Longstreth[167]	149	USA	X		X				
Müller[160]	117	Norway	X	X					
Rautalin[152]	120	Finland	X						
Sandvei[168]	132	Norway	X	X					
Sundström[169]	2659	Sweden	X	X					X

SM = smoking, HT = hypertension, AL = alcohol, OC = oral contraceptives, HRT = hormonal replacement therapy, TC = high total cholesterol, DM = diabetes, BMI = body mass index, ANZ = Australia and New Zealand

also been recognized as risk factors for IA formation.[158, 159] Other unmodifiable risk factors for both the formation and rupture include female sex, age, family history of IAs, ethnicity, and autosomal polycystic kidney disease.[160-162]

2.3.2 Smoking as a cerebrovascular risk factor

Smoking not only increases the risk of IS and PICH, it is associated with many other cerebrovascular diseases, as discussed. Cigarette smoke contains substances which affect the immune and inflammatory response in the brain vasculature. This happens via promoting angiogenesis by upregulating growth factors, such as VEGF, and sustaining a chronic inflammatory state and hypoxia.[170, 171] As mentioned in earlier sections of this book, brain angiogenesis is predominantly driven and mediated by VEGF.[36] VEGF gene transcription is upregulated by various factors, such as hyperglycemia, pro-inflammatory cytokines, and hypoxia.[170, 172] Upregulation leads to endothelial cell proliferation, migration and increase in capillary permeability.[40] Nicotine in cigarette smoke is one of the most studied and distinguished risk factors for IA formation, growth and rupture.[173-176] Additionally, among the 4000 other ingredients in tobacco smoke, reactive oxygen species have been associated with vascular endothelial dysfunction.[177, 178] Nicotine has, in mouse IA models, caused upregulation of mRNA levels of VEGF, PDGF-β and inflammatory cytokines such as interleukin-1, interleukin-6, tumor necrosis factor-α and matrix metalloproteinases (MMP) in cerebral arteries.[172, 179] Downstream from VEGF lies the Ras signaling pathway, ultimately leading to endothelial cell proliferation, migration and the formation of three-dimensional structures in angiogenesis.[36] VEGF also plays an important role in blood–brain barrier dysfunction, and can strongly increase vascular permeability (50,000-fold stronger than histamine).[180] The endothelium dysfunction sets off a cascade of inflammatory responses: the recruitment of leukocytes and the increased secretion of immunoglobulins, complement and other inflammatory and immunologic components.[181]

2.3.3 Modifiable AVM risk factors

The first reported evidence of modifiable risk factors behind AVMs was published in 1998 and it suggested an association between hemorrhagic AVM presentation and hypertension.[182] Probably the largest limitation of this report was the relatively small sample size, as the analysis of hypertension included only 16 patients. The results of this study have not been replicated since. However, it opened up the conversation about the modifiable risk factors behind AVMs. Another risk factor familiar from other cerebrovascular diseases, smoking, has also been a target of some AVM investigators. However, before the publication of our study,[11] the only connection that had been found between AVM patients and smoking was with poor outcome after AVM intervention. The researchers behind these reports have hypothesized that

smoking reduces the likelihood of AVM obliteration when using microsurgery or SRS.[183-185] The study mentioned in the beginning of this section assessed the connection between AVM hemorrhage and smoking, but did not find association.[182] Lifestyle-related risk factors can be difficult to capture because data in patient registries often focus on the clinical aspects. With the rarity of AVMs, this combination of few patients and suboptimal data could explain why the connection between smoking and AVM patients had not been found before the publication of our study.[11]

2.4 Outcome research

2.4.1 Introduction

Probably the most cited and appreciated definition of health was provided by the World Health Organization (WHO) in 1948: ''Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.''[186] Measuring health has always been at the core of medical research.[187] Outcome measures range from the traditional, morbidity- and mortality-focused single-item instruments, to the modern, HRQoL-based health profiles and index scores. Modern medical research is increasingly turning toward the patient-reported outcome measures, whereas in the past it was mostly the clinician who evaluated the outcome at a specified end-point.[188, 189] Nowadays, we can decide from numerous different scales which is the most suitable for our specific research interest. The more commonly used the scale, the more information we have about its behavior in certain scenarios or in statistical handling. The disease-specific tools can be handy in narrow research questions, but can lack sufficient validation regarding rare diseases. Despite being regarded as historical, the single-item outcome instruments measuring physical abilities still have their stronghold in medical research, as objective measures with little confounding factors.[190]

2.4.2 Statistical features of outcome measurement

To evaluate the appropriateness of an outcome instrument, a certain pattern of statistical characteristics needs to be discussed. When testing the instrument in different scenarios, if we are able to recreate the results upon repeated testing, we can call the test instrument reliable (if no change is anticipated). Similarly, if the test is able to differentiate groups based on their results, when this is expected, the instrument is regarded reliable.[191] This feature, sometimes called test–retest repeatability, can be statistically measured with uncertainty analyses.[192] Additionally, another essential feature of reliability is the unchangeability across different interviewers or assessors.[191] Validity measures the level at which the instrument estimates the desired features to be measured. Validation is a process, and therefore validation improves as the instrument is tested in different scenarios by different investigators. In this context, content validity and construct validity can be separated from each other; content

validity describes how well the instrument measures what it is intended to evaluate, and construct validity describes how precisely a nonphysical attribute can be measured by constructing this variable from multiple different sources (for instance, depression, which itself is a sum of certain psychiatric factors). Construct validity, per se, subsumes all other types of validity.[193] The sensitivity of a test can be considered as a sum of discriminatory power and responsiveness. Discriminatory power is the magnitude at which a test can separate results from each other regarding different individuals or patient groups, again when difference actually exists. Responsiveness describes how well the test is able to distinguish changes in test results over time, again if there actually are changes in the results of individuals or groups.[191]

2.4.3 Health-related quality of life

Before discussing HRQoL in more detail, it is essential to distinguish the difference between HRQoL and QoL, which are often used interchangeably.[194] QoL aims to measure not only health-related issues like mobility, symptomalogy, mental well-being, but also social and economic well-being. In this sense, it is much harder to translate into index figures or QoL profiles. Despite being a narrower scale, the HRQoL instruments can cover a significant amount of a person's life and are brilliant indicators of health benefits or the effects of morbidity.[194] Regarding HRQoL, there are various different outcome assessment methods: generic, preference-based and disease-specific instruments.[195] The generic instruments are the most commonly used and can be applied to different morbidities regardless of the study cohort.[196] This also allows the inter-morbid comparison of HRQoL. Preference-based instruments summarize the components of HRQoL into a single index score, usually from 0 to 1, and can therefore be easily applied to cost-effectiveness analyses.[195] The transformation into a single index (or sometimes called utility) score is created using an algorithm with weighted values for each dimension of the HRQoL domains, usually derived from the general population by random sampling. Disease-specific instruments are used and designed for the patient groups harboring a specific illness, and are not therefore as easily adjustable to the general population as the generic instruments, nor do they allow for the comparison between different illnesses.[188] Most of the modern instruments are both generic and preference-based, and by combining both of these features investigators are allowed to compare a specific patient population to the general population, using both the index scores and the HRQoL profiles.[194] The HRQoL instruments measure not only the physical, but also the social and mental domains of health, which play a major role in the financial burden of the morbidity.[197, 198] Notable, however, is that the more complicated real-life variables we aim to measure, the more we need to deal with uncertainties and bias.[188] There is inevitably, to some

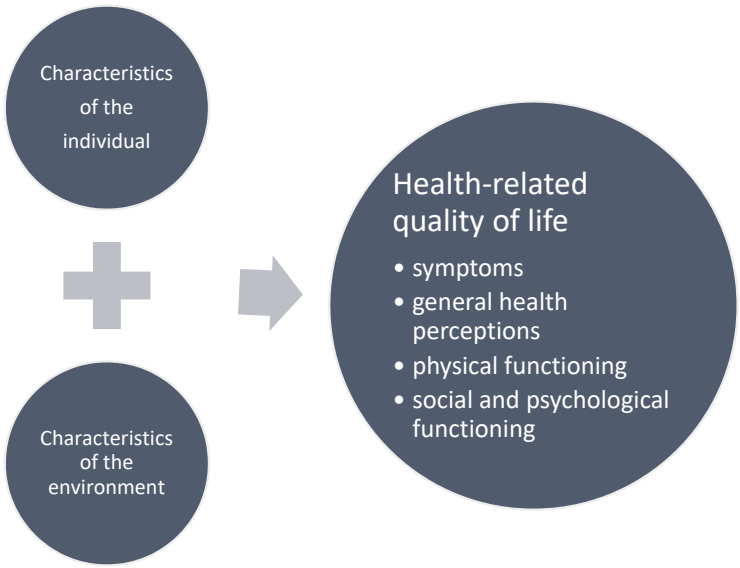

Figure 13. Illustration of the aspects underlying reported health-related quality of life. Adapted from Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA. 1995;273:59-65.

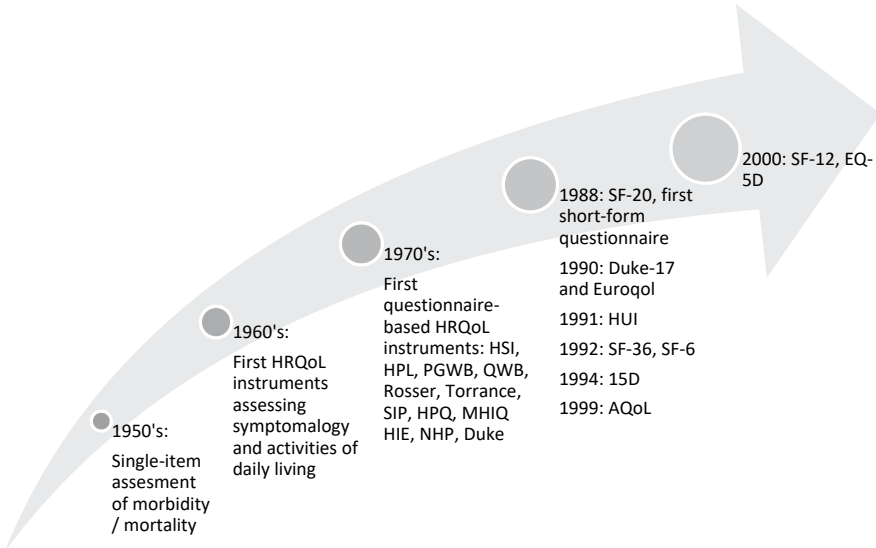

Figure 14. Timeline of the development of HRQoL instruments

extent, environmental and individual characteristics such as religion or culture affecting one's health views, which can complicate generalizability of results across nationalities and cultures (Figure 13).[195]

2.4.3.1 History

The demand for better outcome instruments has existed ever since qualitative medical research began developing in the 1950s.[187, 188] For many years, the definitive outcome for treatment had been reported narrowly, with variables illustrating either morbidity or mortality.[199] Before the 1960s, morbidity assessment was often based on either the functional ability or the activities of daily living, both reported with a single-item score, but in the 1960s, medical literature began discussing QoL.[188, 200] From 1970 to 1981, more than twelve generic HRQoL measures were published.[201] Each of these included multiple health profiles, mainly descriptive and constructed to be used in health services research.[201] However, it was not until the Medical Outcomes Study SF-20 Health Survey in 1988 that the first short-form questionnaires were first introduced.[202] After this, there has been a rapid proliferation of HRQoL instruments. In 2020, the five most-used generic preference-based instruments were the EQ-5D, SF-6D (which can be calculated from SF-12), HUI, 15D and AQoL.[203, 204] Figure 14 illustrates the timeline of the development of HRQoL instruments.

2.4.3.2 15D health-related quality of life instrument

The 15D HRQoL instrument is a generic, self-administered instrument for assessing HRQoL in adults.[205] It can be used both as a profile and as a single index score measure. The questionnaire includes 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental functioning, discomfort and symptoms, depression, distress, vitality, and sexual activity. For each dimension, the respondent chooses one of the five ordinal levels best describing his/her state of health at the moment (best value=1; worst value=5).[205] The single index score (15D score) represents the overall HRQoL on a 0–1 scale (1=full health, 0=being dead) and the dimension level values reflect the goodness of the levels relative to no problems on the dimension (=1) and to being dead (=0). They are calculated from the questionnaire using a set of population-based preference or utility weights. Mean dimension level values are used to draw 15D profiles for groups. A difference in the 15D score of ±0.015 is clinically important.[206] Please see Appendix 1 for the 15D questionnaire form.

2.4.4 Modified Rankin Scale

2.4.4.1 History

The modified Rankin Scale, as the name implies, was developed from the Rankin Scale, originally introduced by Dr. Jon Rankin in 1957, by Dr. van Swieten et

al. in the 1980s.[207] The original scale, numbered from 1 to 5, was generated to measure the degree of disability and dependence after a stroke or any other neurological disease. The adjustment made in the 1980s was the addition of grade 0 to represent patients who lack symptoms and are independent in the activities of daily living. Later in 2005, grade 6 was also added to represent the deceased patients.[208]

2.4.4.2 Use in modern research

The mRS is the most commonly used indicator of functional outcome after stroke.[208] In its current form, it consists of an ordinal classification, in which 0 represents patients with no symptoms and total independence in daily activities; 1 patients with no significant disability, who are able to carry out all usual activities, despite some symptoms; 2 patients with slight disability, who can attend their daily activities without assistance, but who are unable to carry out all previous, premorbid activities; 3 patients with moderate disabilities, who require some help with daily activities but can walk unassisted; 4 patients with moderately severe disability, who cannot attend their own bodily needs without assistance and are unable to walk unassisted; 5 patients with severe disability, who require constant nursing home care and attention, who are bedridden; and 6, deceased patients.[207] mRS is an easy end-point variable in neurosurgical research, however, critique about the interobserver reliability has been expressed by the scientific community.[209] Various educational materials have been developed to unify the grading especially in the mid-grades, in which the differences are substantially smaller than in the end-points of the spectrum.[210] Additionally, since the modern outcome research is turning more toward HRQoL instruments, the developers of mRS have constructed a new version of the original grade, the mRS-9Q, which translates HRQoL-style questions (yes/no) into a single mRS grade.[211] Although promoted as easy-to-administer, the new grade has not, at least yet, proved its popularity among researchers.

2.4.4.3 Dichotomization

Dichotomizing a variable means creating two categories into which the grades from the original variable fall. This is rather common in clinical research, as it for instance eases the presentation of data, the interpretation of the results and the conduction of statistical analyses. However, dichotomization comes with a cost, as it creates a loss of information inside the dichotomous grade, and if the cut-off point is incorrectly chosen might falsify results.[212] It can become especially problematic with follow-up studies evaluating the treatment effect, in which the pursued outcome is getting the patient from the unfavorable outcome group into the favorable outcome group. In this method of evaluating the outcome, we fail to notice improvement inside the dichotomous grade, which might be clinically relevant (Figure 15). The dichotomization of mRS was first used in an acute stroke NINDS (National

Institute of Neurologic Diseases and Stroke) tissue plasminogen (tPA) trial in 1995, in which the grade was cut into a favorable outcome (mRS 0–1) and an unfavorable outcome (mRS 2–5).[213] Ever since the NINDS tPA trial, dichotomization has also become more common in other neurological and neurosurgical studies, with varying cut points. Dichotomization does have multiple statistical advantages.[214] Regarding mRS, it can compensate for the possible issues with interobserver variability, especially in the mid-range of the scale.[212] Owing to its nature as a purely clinical grading system, the cut-off is often chosen to stand at the border of functional independence / dependence.[215] By definition, in mRS 1, the patients can still carry on with their previous activities, whereas in mRS 2 they cannot. Secondly, the mRS 2 patients can still look after their affairs without assistance when compared to mRS 3, and therefore mRS grades ≤2 are defined to indicate functional independence.[216] However, the cut-off points vary between studies, with the rationale behind the decision rarely, if ever, reported. On the other hand, outcomes are rarely dually distributed, complicating the determination of a ''good'' or ''bad'' outcome. This has been

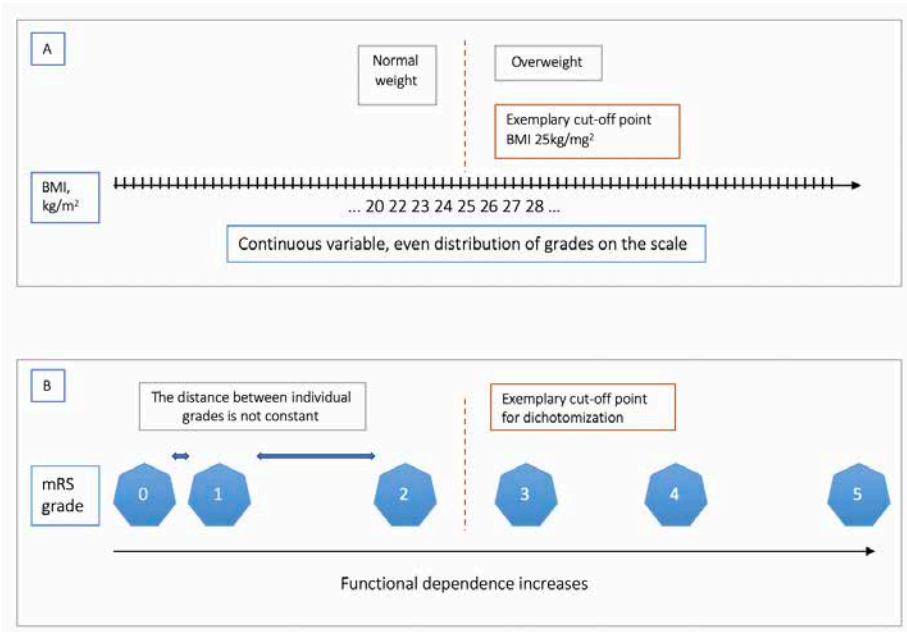

Figure 15A. Example of typical dichotomization of body mass index (BMI): dichotomization of a continuous variable with a commonly recognized cut point.

Figure 15B. Illustration of the problems related with clinical outcome grades and their statistical handling. The gaps between grades are irregular, which complicates the interpretation of results, especially if the cut point is incorrectly chosen. For instance, if the exemplary cut point between mRS 2 and 3 is chosen, but the largest clinical improvement is actually between grades 1 and 2, this effect remains unmasked (loss of information inside the grade). Secondly, if the cut-off point is chosen to be in-between grades very close to each other, for instance grades 0 and 1, there is a higher risk that the improvement / decline between the grades is actually owing to coincidence (bias).

tried to be solved by numerous methods which, rather than comparing two fixed classes to one another, attempt to better take into account the movement across the whole scale.[215, 218] Another issue with mRS dichotomization is that the grades are not evenly distributed concerning the functional outcome, meaning that the distance between patients in mRS 4 and 5 is reportedly longer than for instance between mRS 0 and 1 patients in terms of physical functioning.[219] Therefore, as mentioned, the choice of cut point should support the severity of the disease and the point where the treatment effect is anticipated.[217]

2.4.5 Factors affecting HRQoL

The relationship between HRQoL and functional outcome is well distinguished in the literature.[220, 221] After the transient impact of morbidity starts to diminish and patients' healing progresses, functional outcome improves together with HRQoL.[221] This postmorbid functional, psychological and social improvement can take many years, and the positive effect a close-to-death accident has on the appreciation of life can be influential even decades after.[221] Studies on SAH patients have reported rather significant numbers of patients who have not been able to return to work, as many as two-thirds of the patients even years after the incident.[222, 223] As discussed earlier, the impact returning to work has on QoL and life satisfaction cannot be understated.[224] In a prospective cohort study of 22,000 Finnish working-age people in a 6-year follow-up, the most common reasons for work disability were musculoskeletal and depressive symptoms, and a decrease in vitality.[225] However, in the existing literature about stroke patients, only one study has found an association between depression and inability to return to work.[226] In a Finnish patient sample of aneurysmal SAH (aSAH) patients, the factors associated with long-term employment status after SAH were age inversely, higher levels of education and lower levels of self-rated impairments.[227] Additionally, impaired mental health and functioning have been linked to decreased HRQoL in previous studies on patients with SAH or ICH.[228, 229] This connection has been explained with damage to the reticular formation and related structures of the brain controlling arousal, as well as association to sleeping disorders, stress, pain and chronic illnesses.[230, 231]

3 AIMS OF THE STUDY

1. To evaluate the HRQoL in patients treated for their AVMs and dissect which factors affect this long-term outcome.

2. As smoking is one of the most recognized cerebrovascular risk factors, to evaluate its potential association with brain AVMs.

3. To investigate how an objective outcome instrument (mRS) mirrors the subjective HRQoL and how this could affect the interpretation and statistical handling of the measures.

4 PATIENTS AND METHODS

4.1 Patients and data

During the time of the making of this thesis, the Helsinki AVM Database included 805 patients with brain AVM admitted to the HUH Department of Neurosurgery between 1942 and 2014. The database has been collected retrospectively using medical records and images. The AVM diagnosis was based on angiography (DSA and/or computed tomographic angiography (CTA)). HRQoL questionnaires were sent in 2016 to all living patients (n=432) in the database, older than 18 years of age. The letter contained separate questions regarding symptoms, comorbidities, lifestyle, and self-sufficiency/independence, along with the 15D HRQoL questionnaire. Of them, 325 (75.2%) answered. The anatomical features of the AVMs were evaluated based on CT and/or MR imaging and angiography. The location was classified as either cerebellar, frontal, occipital, parietal, temporal, or deep. The operated patients had follow-up angiograms performed immediately after the surgery to rule out/detect residual AVM. The lesions were classified in SMG, which were converted into SPC, based on their preoperative characteristics.[87, 111] The functional outcome of the patient, measured with mRS, was assessed based on the survey data and clinical records.

4.1.1 Study I

Of the 325 (75.2%) patients who answered the original HRQoL questionnaire, the cohort was further specified to consist of patients with the complete obliteration of the AVM (n=262), regardless of the treatment modality. This was done to minimize the biases owing to patient selection into each treatment modality, since with modern knowledge the best possible modality is chosen for the patient, causing inevitable selection bias. The general population sample was obtained from the HUH catchment with the Finnish Health 2011 Survey.[232]

4.1.1.1 Engel classification for postoperative epilepsy

In Study I, we used the Engel classification for postoperative epilepsy, which has been proposed in 1993 by neurologist Jerome Engel.[233] It has become the most used scale demonstrating the outcome after epileptic surgery.[234] The grading is based on the self-reported symptomalogy of the patient. By definition, Engel class I patients are free of disabling seizures; class II patients have disabling seizures rarely, during a period of at least two years; class III patients experience a notable improvement and seizure reduction for prolonged periods, however for less than two years; and class IV in which patients have not noticed any reduction

in the seizures, or some reduction but not notable improvement.[233]

4.1.2 Study II

Patients were derived from the Helsinki AVM HRQoL database. Patients younger than 18 years of age during admission were excluded from the study to ascertain a sufficient exposure time to cigarette smoking before admission. This meant excluding 48 patients, leaving the final study cohort of 277 patients. The HRQoL letter included a panel of questions about lifestyle and demographic, socioeconomic and behavioral aspects. The letter included questions about smoking status at the time of answering the questionnaire (current/ex/never-smoker), the number of cigarettes smoked daily, and the length of smoking history in years. These data, supplemented with the data from clinical records, were used to determine patients who were smoking during admission or during the follow-up period and had a smoking history of at least one year. The same criterion of the length of smoking was used as an inclusion criterion for the analysis of the smoking prevalence, thus, the patients had to have at least one year of a smoking history before the admission. When the clinical records were explored, eight more patients were found who had smoked more than one year continuously before their diagnosis, and they were classified as on-admission smokers, and included in the prevalence analyses. Despite the exploration of clinical records, a total of 65 (24%) patients who were smoking at the time of the questionnaire or had a smoking history had not reported the length of their smoking history and could not reliably be classified as on-admission smokers. This was to provide a conservative estimation and to avoid exaggerating the prevalence of on-admission smokers. However, presumably some of these patients were smoking already during their admission. For the cross-tabulations of the demographic characteristics of the study cohort, patients had to have at least one year of continuous smoking during the follow-up period to be regarded as ever-smokers. Only one patient had smoked less than one year continuously and was classified as a never-smoker. The matched prevalence was obtained from the statistics of the National Institute of Health and Welfare in their yearly random sample of the Finnish population.[235]

4.1.3 Study III

Of the 325 patients who answered the HRQoL letter, only two had an mRS 5 functional status in 2016. Owing to the scarcity of these patients, they were excluded from the final study cohort, leaving 323 patients for the analyses. Since the main idea of the study was to illustrate how the different mRS grades reflect HRQoL, there was no need for making further specifications to the mRS cohorts, since in fact these factors (such as treatment modality) should not affect the mRS classification directly. Two patients (0.9%) had not filled in the whole 15D questionnaire, and therefore they were excluded from the analyses of the dimensions in question. The 15D data

for the reference group came from the Finnish National Health 2011 Survey, which represents Finnish citizens over 18 years of age collected with random sampling from the general population. This group was selected from the HUH catchment area (n=1350) to rule out possible biasing factors, such as cultural differences. For the literature review, we collected all the AVM studies from the previous five years which had used dichotomized mRS in their analyses. This was done by searching PubMed with the search terms ''AVM'', ''arteriovenous malformation'', ''mRS'', ''modified Rankin Scale'' and ''functional outcome'' on 2 August 2020. Studies which had reported the dichotomization, follow-up time and number of patients were included. We excluded studies with pediatric or elderly AVM patients. The 15D data for the general population came from the National Health 2011 Survey representing the Finnish population aged over 18.[232]

4.2 Statistical methods

4.2.1 Studies I and III

We used the generic, self-administered 15D HRQoL instrument to illustrate the differences in the long-term HRQoL.[205] The results obtained with the 15D were compared with those of the general population (n=1347) standardized for age and gender, and obtained from the HUH catchment area of the Finnish Health 2011 Survey.[232] The statistical analysis was performed using the SPSS for Mac statistical software version 24 (SPSS, Inc., Chicago, IL, USA). Subgroup 15D analyses were conducted for the variables of SPC (for groups SPC A, B, and C), number of bleeding episodes (for zero, one, or multiple bleeding episodes), epilepsy (groups Engel I and II–IV), mRS (grades 0–4 independently) and lesion's anatomical location (classified as mentioned above). Quantitative variables were handled as continuous or ordinal, with the exception of the number of bleeding episodes variable, for which the patients with multiple (two or more) bleeding episodes comprised their own group, compared to patients with only one or no bleeding episodes. The statistical significance of the differences in the mean HRQoL scores and its dimensions were tested by independent samples t-test or analysis of covariance (ANCOVA) (age-standardized), followed by Bonferroni-corrected post-hoc tests. The variance in the 15D scores was explained by a Tobit regression model.[236] The model was deemed suitable for two reasons. First, the distribution of the dependent variable (15D score) was not normal but skewed and censored at 0 and 1 (the range of the scores is 0–1) and, second, a substantial proportion of the observations was at the upper limit of 1 (19.8%). The Tobit regression model was run by LIMDEP version 7.0 (Greene WH. LIMDEP Version 7.0: User's manual, revised version. Econometric Software, Inc.: New York, 1998). Variables included in the regression model were patient's age at admission, sex, bleeding status at admission, SPC, and refractory epilepsy. The reference groups for the nominal variables in the model were male sex, SPC group B, and the group with no

bleeding episodes. Two-sided p-values <0.05 were considered statistically significant.

4.2.2 Study II

Because a large proportion of all AVMs in Finland have been treated in our clinic in Helsinki, we compared the on-admission smoking prevalence in AVM patients to that of the general population. AVM admission year and sex-matched prevalence of smokers in the general population was derived from statistics of the National Institute for Health and Welfare that includes yearly random samples of the general population.[235]e> The final age group–specific general population data included the same proportion of men and women as the AVM data. In addition, the data collection years had the same distribution as AVM patients' admission years. This was done to take into account the changes in smoking prevalence over the data collection period. Logit transformation of proportions and Students t distribution were used to calculate the 95% CIs for prevalence estimates. We categorized smokers to light (less than 10 cigarettes per day), moderate (from 10 to 19 cigarettes per day), and heavy smokers (20 or more cigarettes per day). Difference between variables with two categories was tested with Fisher's Exact test with two-sided p-values, and variables with three categories with Kruskal–Wallis H test. For normally distributed continuous variables, we used independent samples t test. Mann–Whitney U test was used for the analyses of the differences in the number of daily cigarettes for the following grouping variables: sex, age group at admission, age group in 2016, admission decade, AVM size (descriptive: small being 0–1 inches vs. medium 1–2 inches vs. large >2 inches), pattern of venous drainage (superficial vs. deep vs. superficial and deep), AVM location (deep vs. cortical vs. cerebellar), number of AVM hemorrhage (zero vs. one bleeding episode vs. more than one), and mRS in 2016. P-values <0.05 were considered statistically significant. Statistical analyses were conducted using Stata/MP15.1. Stata Corp, College Station, TX, USA and A.P using IBM SPSS Version 24.0.0.0 for Mac (SPSS, Inc., Chicago, IL, USA).

4.3 Standard protocol approvals

All individual participants gave informed consent for the use of questionnaire data in the studies in this thesis project. The studies were approved by the ethics committee of HUH.

5 RESULTS

5.1 Demographic characteristics

5.1.1 Study I

The mean age during admission was 35.2 years (SD ±16.4yr) and in 2016 52.8 years (SD ±15.3yr).[I] The mean follow-up time from the diagnosis to 2016 was 17.6 years (SD ±12.0 yr). Table 7 collects the demographic characteristics of the cohort of Study I. Comorbid conditions were reported by 191 patients (72.9%); the most common diagnosis was hypertension (26.7%), followed by epilepsy (14.5%) and transient ischemic attack (9.5%).[I] The AVM had affected the vocational selection of 44 patients (16.8%). Forty-one patients (15.6%) had retired due to the lesion and 59 patients (22.5%) due to age.

There were 33 patients (12.6%) with associated aneurysms.[I] The rest of the anatomic characteristics are given in Table 8. A total obliteration was achieved in all patients (the criterion for the cohort), and this was accomplished with neurosurgery in 249 patients (95.0%). Embolization was included in the treatment plan in 25 SPC A patients, 9 SPC B patients and 5 SPC C patients; and SRS in 5 SPC A, 9 SPC B and 5 SPC C patients.[II] Of the 137 SPC A patients, 135 were operated on (98.5%), of 80 SPC B patients 73 were operated on (91.3%) and of 42 SPC C patients 41 were operated on (97.6%). This is mostly due to the fact that the criterion for inclusion in this study was the total occlusion of the lesion, for which surgery is the most effective method.

5.1.2 Study II

The mean age on admission was 38.8 years (SD ±14.8yr) and in 2016 57.0 years (SD ±14.5yr).[II] The demographics and anatomic lesion characteristics are reported in Table 9. Sixty-four (23.1%) patients were admitted before the 1990s, 66 (23.8%) during the 1990s, most patients were admitted during the 2000s (n=100, 36.1%) and 47 (17.0%) patients after 2010.[II]

5.1.3 Study III

The mean follow-up time from admission to 2016 was 19.4 years (SD=±13.8 years) (Table 8). All patients had had at least one-year follow-up before returning the questionnaire. The longest follow-up time was 63 years. Table 10 illustrates the basic demographic characteristics of each mRS cohort.

Table 7. Demographic characteristics of Study I.

		n	%
Sex	Female	127	48.5
	Male	135	51.5
	Total	**262**	**100.0**
Admission decade	Before 90's	55	21.0
	1990s	67	25.6
	2000s	101	38.5
	2010s	39	14.9
	Total	**262**	**100.0**
Education	Basic level	59	22.5
	Vocational	61	25.3
	High school	26	9.9
	Polytechnic	75	28.6
	University	36	13.7
	Total	**262**	**100.0**

Table 8. Anatomic characteristics AVMs in Study I. Infratentorial lesions include both brainstem and cerebellar lesions.

		n	%
Preoperative SPC	A	139	53.3
	B	80	30.7
	C	42	16.1
	Total	**261**	**99.1**
Location of the lesion	Infratentorial	56	21.4
	Frontal	80	30.5
	Occipital	26	9.9
	Parietal	47	17.9
	Temporal	51	19.5
	Multiple	1	0.4
	Total	**261**	**99.6**
Ruptured AVM	No	74	28.2
	Yes	187	71.9
	Single bleeding ep	*162*	*61.8*
	More than 1	*25*	*9.5*
	Total	**262**	**100.0**

Table 9. Demographic and anatomic characteristics of Study II.

		n	%
Sex	Female	136	49.1
	Male	141	50.9
	Total	**277**	**100.0**
Rupture status	Ruptured	179	64.6
	Unruptured	98	35.4
	Total	**277**	**100.0**
Operated	Yes	224	80.9
	No	53	19.1
	Total	**277**	**100.0**
AVM size	Small (0-1 inch)	131	47.3
	Medium (1-2 inch)	114	41.2
	Large (>2inch)	32	11.6
	Total	**277**	**100.0**

Table 10. Demographic characteristics of study III.

	Females	AVM fully occluded	Mean age in 2016 (years)	Mean age during admission (years)	Mean follow-up time (years)	Follow-up time range (years)
mRS 0						
N=154	61 (40%)	128 (82%)	52.5 SD=±16.1	32.4 SD=±15.3	18.9 SD=±13.0	1.7-63
mRS 1						
N=78	44 (56%)	62 (80%)	50.9 SD=±16.4	35.8 SD=±17.4	22.0 SD=±15.6	1.2-62
mRS 2						
N=39	20 (51%)	28 (72%)	56.5 SD=±16.5	32.1 SD=±13.8	16.5 SD=±11.8	1.3-52
mRS 3						
N=32	21 (66%)	28 (88%)	56.8 SD=±15.0	38.0 SD=±18.8	19.6 SD=±11.7	1.3-50
mRS 4						
N=20	13 (62%)	18 (86%)	67.1 SD=±8.9	48.7 SD=±18.3	23.5 SD=±20.0	1.4-59
Total						
N=323	159 (49%)	262 (81%)	54.0 SD=±16.2	34.7 SD=±16.6	19.4 SD=±13.8	1.2-63

5.2 Long-term health-related quality of life in 262 patients

Compared to the general population using age- and sex-standardization, AVM patients with totally occluded lesions (n=262) had impaired HRQoL, with a mean difference (MD) in 15D index score of 0.047 (95% CI: 0.032–0.062, p<0.0001). This is illustrated in the 15D profile in Figure 16, which also separates the independent dimensions. The largest impairments were in the dimensions of usual activities, movement, mentality and sexual activity.[I]

5.2.1 SPC classification and HRQoL

In the AVM patients with totally occluded lesions, the patients with SPC A type lesions had a significantly better HRQoL in long-term follow-up compared to the patients with SPC C type lesions (MD=0.0646, 95% CI: 0.018–0.112, p=0.0031). Regarding the 15D index score, SPC B and SPC C did not differ statistically significantly (MD=0.0442, 95% CI: -0.006–0.095, p=0.109), however, there were significant differences in the individual dimensions (vision, speech, discomfort) as illustrated in Figure 17. The characteristics of patients in SPC classes are given in Table 11.

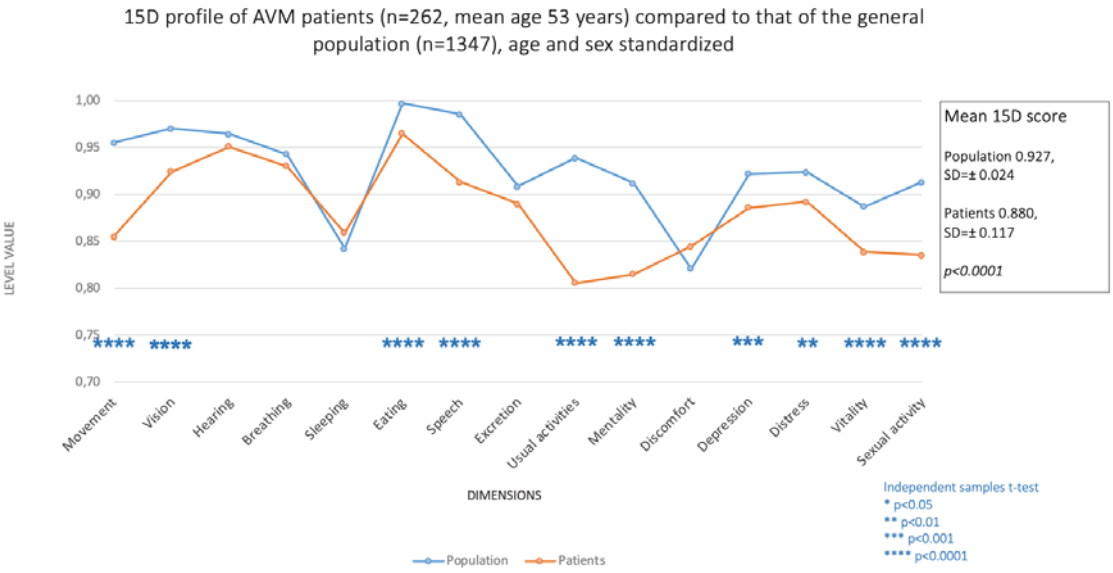

Figure 16. 15D profiles of AVM patients with totally occluded lesions (n=262) compared to that of the general population (n=1347) using age and sex standardization. Asterisks indicate statistical significance in the dimension in question, tested with the independent samples t test. Patients with missing values in the dimension in question were not included in the analysis of that dimension.

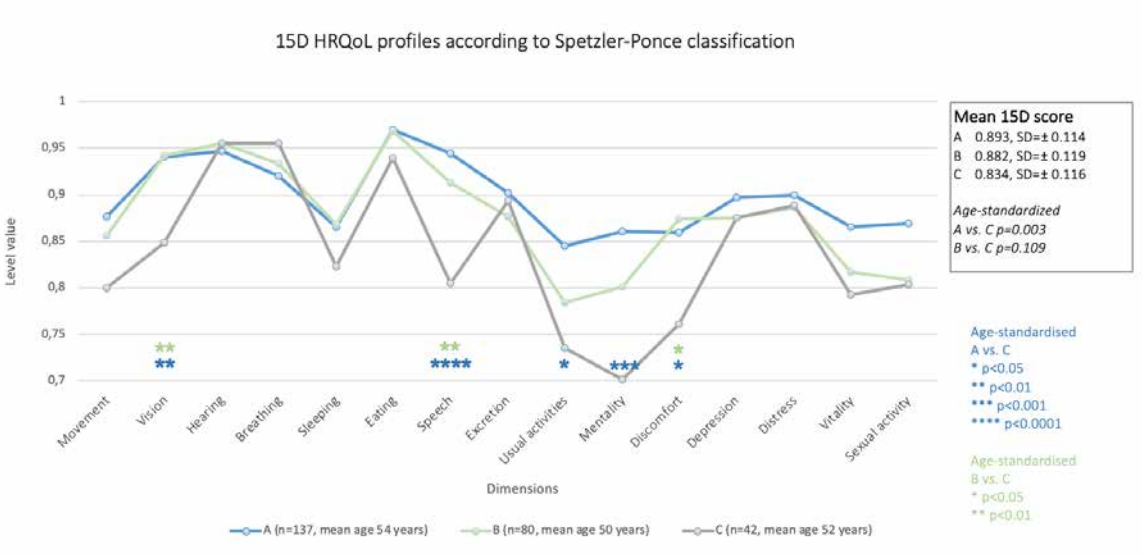

Figure 17. Comparison of 15D HRQoL profiles according to SPC classes. Statistical significance in the individual comparisons between classes in each HRQoL dimension is marked with asterisks. The comparison of index scores (mean 15D score) and the statistical significance of this comparison is reported in the table in the upper-right corner. One patient with missing SPC grade was excluded from these analyses.

5.2.2 Number of bleeding episodes

Multiple bleeding episodes were associated with a decreased HRQoL, however, this difference, compared to a single bleeding episode or no hemorrhagic events, did not yield statistical significance.[I] The MD of the 15D index score between a single bleeding episode and no bleeding episodes was 0.031 (95% CI: -0.007–0.069, p=0.146), between a single bleeding episode and multiple (>1) episodes 0.03 (95% CI: -0.029–0.089, p=0.647), and between no bleeding episodes and multiple bleeding episodes 0.061 (95% CI: -0.001–0.124, p=0.057).[I] In the comparisons of the individual dimensions, there were statistically significant differences between the group of patients with no bleeding episodes and the group with multiple bleeding episodes in the dimensions of vision and usual activities (Figure 18).

5.2.3 Postoperative epilepsy and HRQoL

Postoperatively, there were 38 patients (14.5%) who had Engel class II–IV epileptic seizures at the time of the survey. The dimensions which were impaired the most were mental functioning, usual activities and vitality.[I] Compared to Engel class I patients, the MD was 0.061 (95% CI: 0.023–0.100, p=0.00017). These 15D HRQoL profiles are illustrated in Figure 19.

Table 11. Characteristics of AVM patients in each SPC category.

		N/o bleeding episodes			SPC x n/o bleeding episodes, Fisher's Exact test, 2-sided p=0.014
Preoperative SPC		0, n (%)	1, n (%)	>1, n (%)	Total, n (%)
	A	29 (39.2)	98 (60.5)	12 (48.0)	139 (53.3)
	B	31 (41.9)	43 (26.5)	6 (24.0)	80 (30.7)
	C	14 (18.9)	21 (13.0)	7 (28.0)	42 (16.1)
Total (%)		74 (28.2)	162 (61.8)	25 (9.5)	261 (99.6)
		SPC A	**SPC B**	**SPC C**	ANOVA
Mean (SD) age at admission, years		36.7 (17.2)	33.1 (16.1)	33.6 (13.8)	F(2, 258)=1.45, 2-sided p=0.237
Mean (SD) age in 2016, years		54.4 (15.7)	50.4 (15.4)	51.9 (13.2)	F(2, 258)=1.86, 2-sided p=0.158
					Fisher's exact test, 2-sided p
Females (%)		70 (50.4)	35 (43.8)	22 (52.4)	P=0.575
Retired due to AVM (%)		16 (11.5)	12 (15.0)	13 (31.7)	P=0.018
Symptoms due to AVM		85 (61.2)	54 (67.5)	34 (81.0)	P=0.051
Treatment included:					
Surgery (%)		135 (97.1)	73 (91.3)	41 (97.6)	P=0.130
Embolization (%)		25 (18.0)	27 (33.8)	26 (61.9)	p<0.0001
Radiosurgery (%)		5 (3.6)	9 (11.3)	5 (11.9)	P=0.038
mRS at last follow-up					$\chi 2(2,255) = 10.06$, p=0.0070
0 (%)		47 (35.1)	28 (35.0)	8 (19.5)	
1 (%)		39 (29.1)	20 (25.0)	7 (17.1)	
2 (%)		31 (23.1)	19 (23.8)	13 (31.7)	
3 (%)		11 (8.2)	8 (19.5)	9 (22.0)	
4 (%)		5 (3.7)	5 (6.3)	3 (7.3)	
5 (%)		1 (0.7)	0 (0)	1 (2.4)	
ANOVA = analysis of covariance					

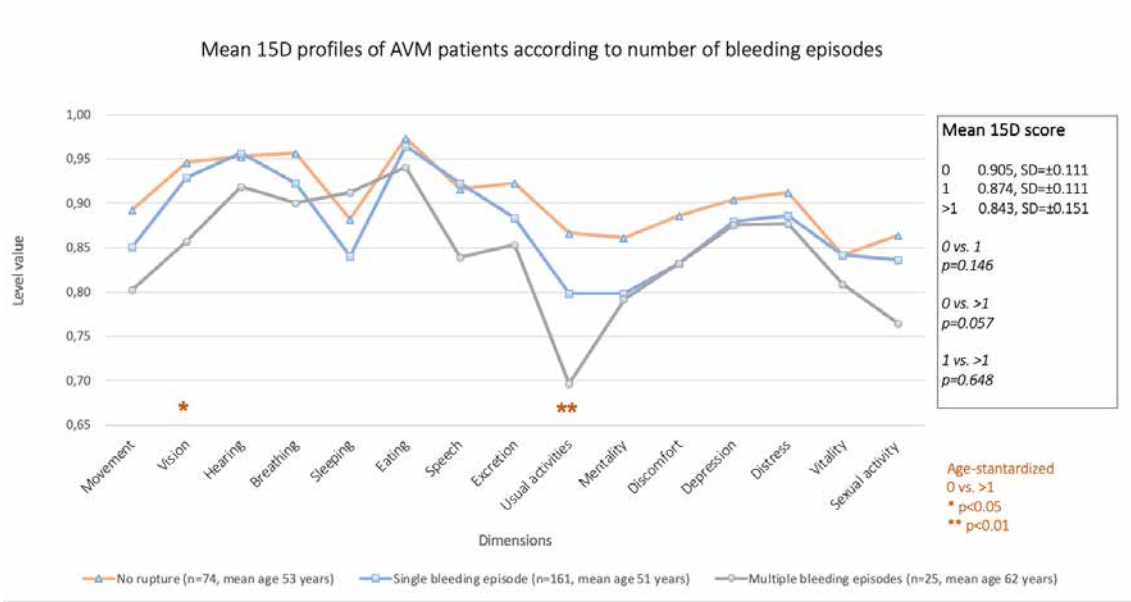

Figure 18. Comparison between patients with no bleeding episodes from the AVM, patients with a single bleeding episode and patients with more than one (multiple) bleeding episodes. The only statistically significant differences were in the dimensions of vision and usual activities between patients with no bleeding episodes and patients with multiple bleeding episodes. Despite the statistical non-significance of the rest of the dimensions, there is a clear trend toward worse HRQoL values owing to multiple bleeding episodes.

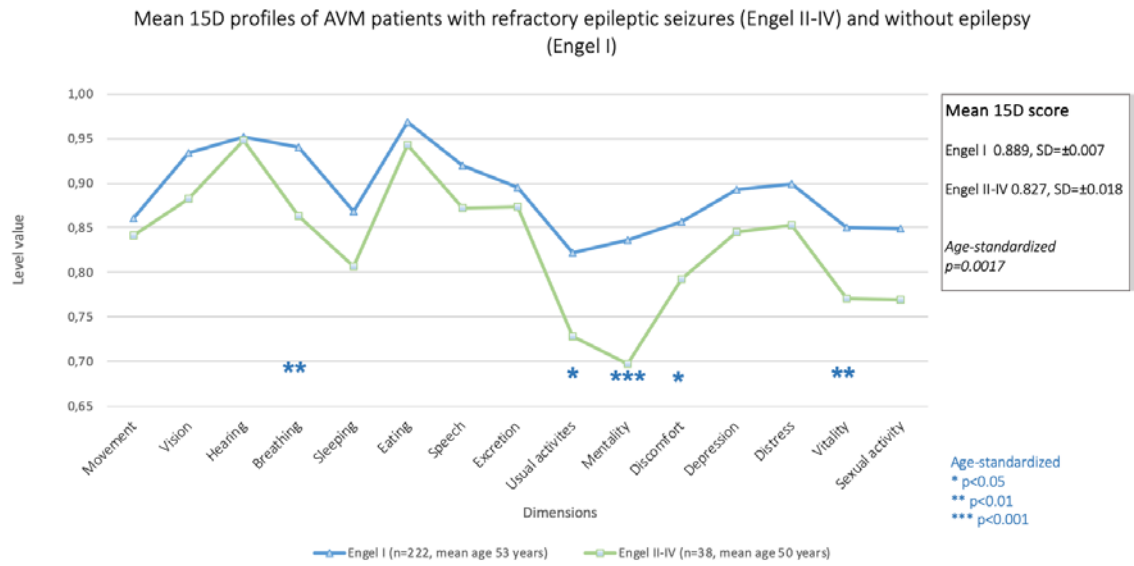

Figure 19. Comparison between patients with refractory epilepsy (Engel II–IV) and patients without epilepsy (Engel I). By definition, Engel class I patients are free of disabling seizures. For more specific definitions, please see section 2.1.6.7.

5.2.4 Location of the lesion

The HRQoL did not differ regarding the different cortical locations. However, there was a significant decrease in the total 15D score of the patients with deeply located lesions compared to the frontal (MD 0.086, 95% CI: 0.013–0.159, p=0.008), parietal (MD 0.094, 95% CI: 0.014–0.174, p=0.007), and temporal (MD 0.087, 95% CI: 0.004–0.165, p=0.016) AVMs. Also, decreased mental functioning was associated with deeply located AVMs (mean 0.622, SD ±0.238) compared to those with frontal (MD 0.232, 95% CI: 0.079–0.385, p<0.0001), parietal (MD 0.227, 95% CI: 0.060–0.395, p=0.001), temporal (MD 0.229, 95% CI: 0.065–0.394, p=0.001), and cerebellar (MD 0.192, 95% CI: 0.001–0.383, p=0.047) lesions. Another dimension with decreased values among the patients with deep AVMs was the ability to continue previous usual activities (mean 0.689, SD ±0.254 for deep AVMs) compared to those with frontal (MD 0.140, 95% CI: -0.023 to 0.303), parietal (MD 0.180, 95% CI: -0.002 to 0.359), and temporal (MD 0.174, 95% CI: -0.001 to 0.349) AVMs. These differences, however, did not reach statistical significance.

5.2.5 Functional outcome and HRQoL

The effect functional outcome, measured with mRS, has on long-term HRQoL was evaluated in patients with totally occluded lesions.[1] At the last follow-up there were 83 patients (31.7%) in mRS 0, 67 in mRS 1 (25.6%), 63 in mRS 2 (24.0%), 28 in mRS 3 (10.7%), 13 in mRS 4 (5.0%) and 2 in mRS 5 (0.8%). Higher mRS scores (decrease in functional outcome) were associated with decreased HRQoL: mRS score of 0 (mean 15D 0.938, SD ±0.082, mean age 49 years), mRS score of 1 (mean 0.895, SD ±0.118, mean age 53 years), mRS score of 2 (mean 0.869, SD ±0.087, mean age 52 years), mRS score of 3 (mean 0.771, SD ±0.129, mean age 60 years), and mRS score of 4 (mean 0.721, SD ±0.116, mean age 61 years). There was no statistically significant difference in the mean 15D score between the patients in mRS 0 and mRS 1, nor in mRS scores of 1 and 2 or scores of 3 and 4. All other scores reached statistical significance in the pairwise comparisons of total 15D score (p<0.002). There was a significant difference between the different mRS grades in the physical dimensions (movement, usual activities and sexual activity). The mental domains overlapped in all the other grades except mRS 0.

5.2.6 Multivariate model predicting long-term HRQoL in treated AVM patients

We used Tobit regression to estimate the 15D index (total) score based on age, sex, refractory epilepsy, SPC, and number of bleeding episodes. We found a significant regression equation ($F_{7,251}$= 9.37, p<0.0001), with an R^2 of 0.207: patient's index 15D score = 0.8497 – 0.00234(age in years, p<0.0001) + 0.0365(if male, p<0.0044) – 0.0530(if Engel II–IV, p<0.0034) – 0.0402(if SPC C, p<0.0388) – 0.0548(if multiple bleeding episodes, p<0.0217). There was no statistically significant difference in the equation

between the patients having SPC A or SPC B lesions.

5.3 The association between smoking and AVM patients

In the HRQoL questionnaire, we inquired about the smoking habits of AVM patients. These data were supplemented with the exploration of clinical records. Despite this, the length of smoking history could not be determined for 66 patients. Table 12 illustrates the smoking statistics derived from the questionnaire supplemented with clinical records. When taking into account the patients of all ages, the proportion of smokers in AVM patients was 48% (95% CI: 41–55%) during admission, whereas in the age-, sex- and admission year–matched general population 19% (95% CI: 16–21%). The difference increased in the older patient groups: in the age group of 20–34 years, the mean percentage of smokers in AVM patients was 33% (95% CI: 21–49%), whereas the general population mean was 20% (95% CI: 18–23%); age group 35–44 years, AVM patients' mean 52% (95% CI: 38–67%) and population mean 20% (95% CI: 17–23%); age group 45–54 years, AVM patients' mean 57% (95% CI: 41–72%) and population mean 20% (95% CI: 17–23%); age group 55–64 years, AVM patients' mean 53% (95% CI: 36–70%) and population mean 16% (95% CI: 14–20%); and age group 65–77 years, AVM patients' mean 73% (95% CI: 46–90%) and population mean 7% (95% CI: 5–9%).[II] These differences are illustrated in Figure 20.

In the univariate analyses, females smoked less daily (mean 11.3 cigarettes, SD ±8.1) than male AVM patients (mean 14.0 cigarettes, SD ±9.2), p=0.020). A small AVM size was associated with less cigarettes smoked daily (mean 11.6 cigarettes, SD ±8.5) compared to the patients with medium (mean 13.8 cigarettes, SD ±9.6) or large AVMS (mean 13.9, SD ±6.0), however, these differences did not reach statistical significance. All the patients who still continued smoking in 2016 despite AVM diagnosis / treatment (n=66) were mostly either moderate (31.8%) or heavy smokers (34.1%).[II]

Table 12. Smoking statistics derived from the HRQoL questionnaire sent in 2016, supplemented with data from clinical records. The categories for the number of cigarettes smoked daily were as follows: less than 10 cigarettes for light smokers; 10–19 cigarettes per day for moderate, and 20 or more cigarettes for the heavy smokers.

		N	%
Smoking before admission	Yes	105	37.9
	No	106	38.3
	Not known	66	23.8
	Total	**277**	**100**
Smoking ever	Never	98	35.4
	Current or ex	179	64.6
	Total	277	100
Smoking in 2016	Yes	66	23.8
	No	211	76.2
	Total	**277**	**100**
Number of daily cigarettes	Light smoker	41	22.9
	Moderate	57	31.8
	Heavy	61	34.1
	Total (of all ever-smokers)	**159**	**88.8**

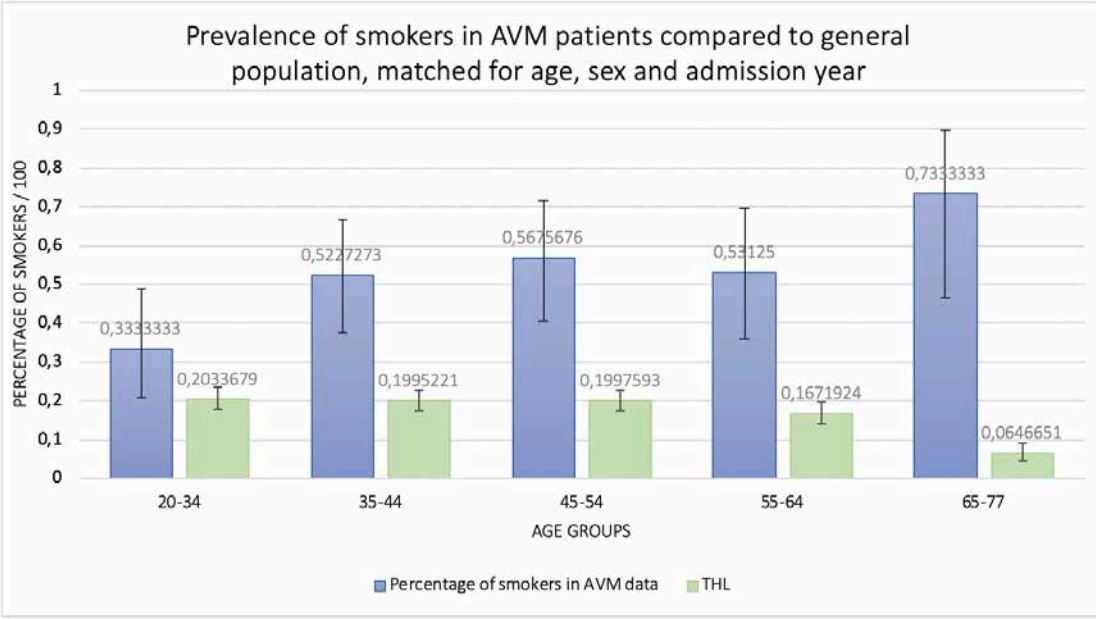

Figure 20. Prevalence of smokers in AVM patients and the general population, matched for age, sex and admission year. Prevalence is reported with the percentage of smokers / 100 (i.e., 30% = 0.3). Blue bars represent AVM patients and green bars (THL) the matched general population. 95% CIs are reported with the whiskers. The figure was drawn with the conservative estimation, meaning that the patients whose length of smoking could not be reliably estimated (n=66) were classified as non-smokers. Of them, 11 were smoking in 2016 and 54 were ex-smokers.

5.4 Health-related quality of life and modified Rankin Scale

5.4.1 Comparison of mRS grades and the general population

There were 154 AVM patients with a functional outcome of mRS 0 in 2016, and their mean 15D score was 0.954 (SD ±0.060). Compared to the age- and sex-standardized general population (mean 15D index score 0.927, SD ±0.028), they had a better 15D index score and this difference was statistically significant ($p<0.0001$). These profiles are illustrated in Figure 21. Patients with an mRS 1 functional outcome in 2016 (mean 15D index score 0.844, SD ±0.100) had worse HRQoL than the age- and sex-standardized general population (mean 15D index score 0.927, SD ±0.021), and this difference was statistically significant ($p<0.0001$). These profiles are illustrated in Figure 22.

5.4.2 Comparing mRS grades to each another

All of the mRS grades included in this study were compared to each other regarding HRQoL in 2016 measured with 15D. The grades differed significantly from each other regarding their 15D index score, with the exception of mRS 1 (mean = 0.840, 95% CI: 0.821–0.860) and mRS 2 (mean = 0.841, 95% CI: 0.813–0.868). Mobility was the only individual dimension which was able to distinguish the grades from each other. The estimated mean values for the mobility dimension were 0.968 (95% CI: 0.946–0.991) for mRS 0 patients, 0.885 (95% CI: 0.853–0.916) for mRS 1, 0.783 (95% CI: 0.738–0.827) for mRS 2, 0.662 (95% CI: 0.613–0.711) for mRS 3, and 0.311 (95% CI: 0.246–0.376) for mRS 4. Figure 23 illustrates the comparison between mRS grades. Figure 24 illustrates the comparison of 15D scores between mRS 0 and mRS 1 AVM patients using age and sex standardization. 95% CIs are included in the figure.

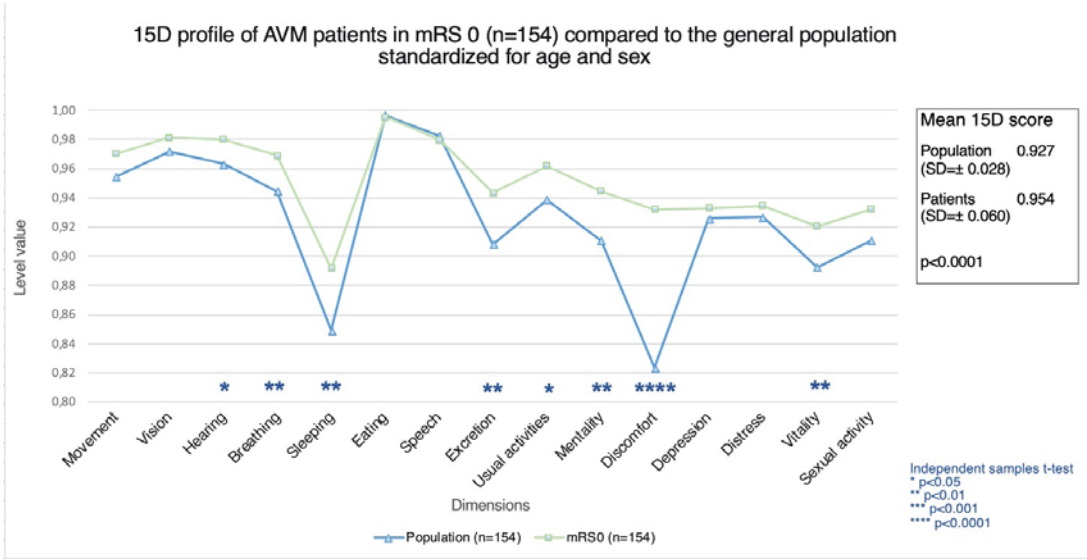

Figure 21. Patients with mRS 0 functional status in 2016 compared to the age- and sex-standardized general population regarding their answers to the 15D HRQoL questionnaire. The difference between the index 15D scores was statistically significant, as well as the individual dimensions marked with asterisks.

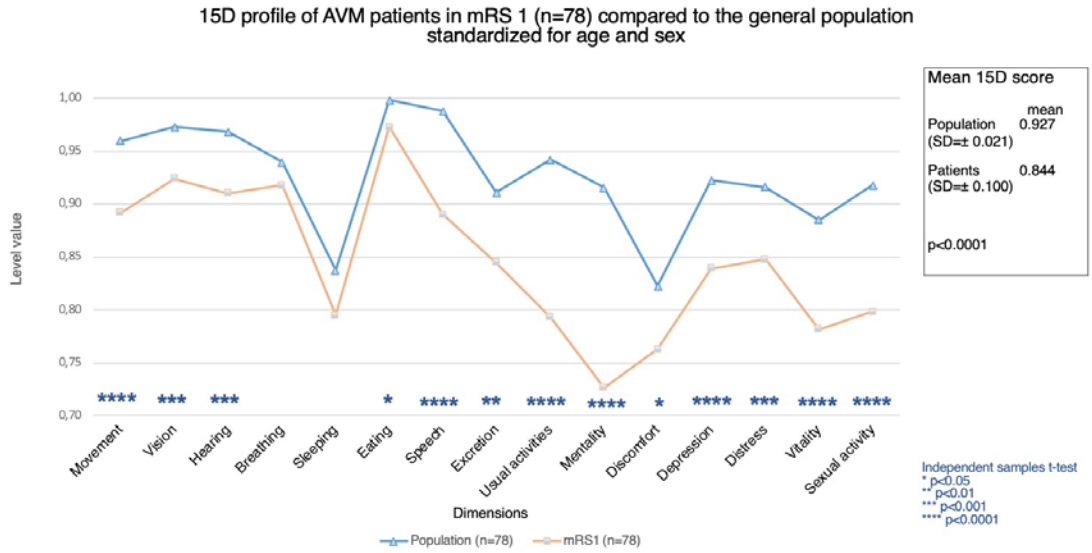

Figure 22. Comparison of patients with mRS 1 functional status in 2016 and the general population (age- and sex-standardized) regarding HRQoL measured with 15D. The difference between index 15D was statistically significant, as well as the individual dimensions marked with asterisks.

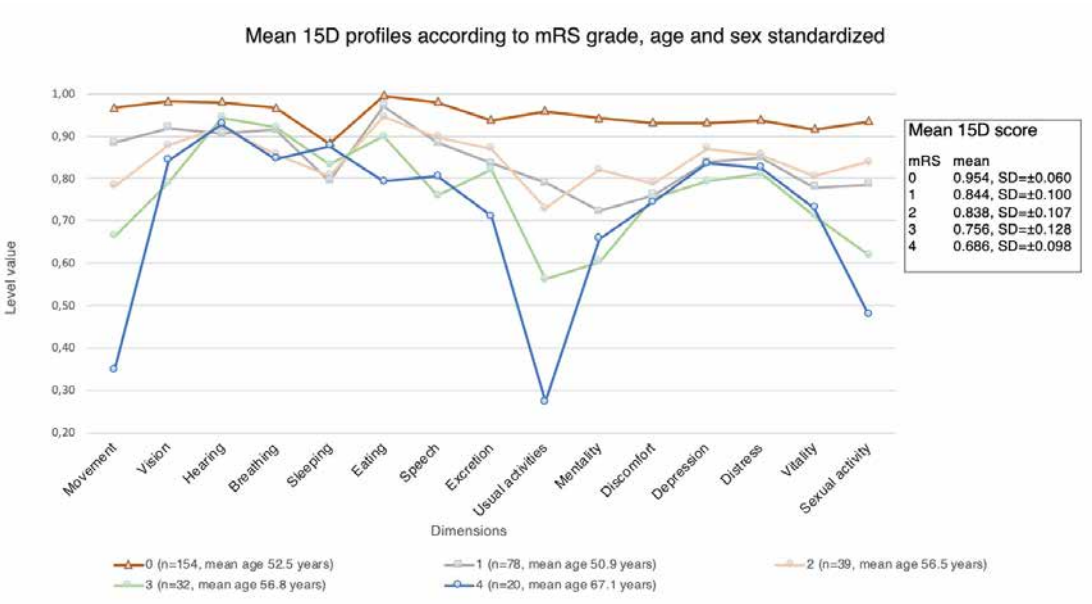

Figure 23. Comparison of mRS grades to each other using age and sex standardization. In the dimension of usual activities, all the grades, except mRS 1 and 2, differed statistically significantly from one another: the estimated means for this dimension were 0.959 (95% CI: 0.932–0.986) for mRS 0 patients, 0.790 (95% CI: 0.753–0.828) for mRS 1, 0.730 (95% CI: 0.676–0.783) for mRS 2, 0.561 (95% CI: 0.503–0.620) for mRS 3 and 0.283 (95% CI: 0.206–0.360) for mRS 4. All the mRS grades differed statistically significantly from each other regarding the index 15D score, except mRS 1 and mRS 2.

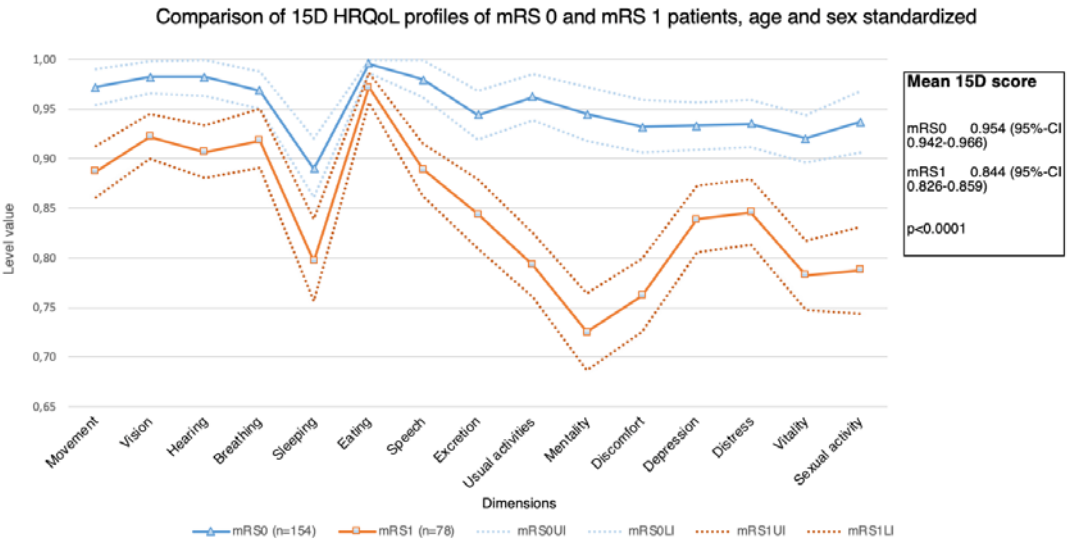

Figure 24. Comparison of the 15D scores in mRS 0 and mRS 1 AVM patients, age- and sex-standardized. 95% CIs are illustrated with dots, UI = 95% CI upper margin, LI = 95% CI lower margin.

5.4.3 Literature review

All the 17 AVM follow-up studies using mRS dichotomization published within the previous 5 years are represented in Table 13. Nine studies (52.9%) categorized favorable outcomes as mRS 0–2 and unfavorable as mRS 3–5.[86, 120-123, 130, 131, 237, 238] The rest (47.1%) used the lower cut point of mRS 1.[50, 82, 85, 118, 119, 239-241] All the studies with either high-grade or brainstem AVMs used the higher cut point.[86, 122, 238] In the studies using the cut point of mRS 2, the mean follow-up time was 3.4 years (SD ±3.1y), and for the studies using the cut point mRS 1, 2.4 years (SD ±1.9y).

Table 13. AVM studies using dichotomized mRS published in the previous 5 years. Studies with low-grade or cerebral AVMs had the tendency of using a lower cut point, whereas in studies with infratentorial, deep or high-grade AVMs the higher cut point was chosen.

Author (year)	Mean follow-up time (years)	Favorable mRS	Sample size	AVM lesion characteristics
Wang et al. (2020)[131]	4.5	0-2	258	Low-grade, SMG I-II AVMs
Pulli et al. (2019)[82]	5.0	0-1	318	Cerebral AVMs
Iosif et al. (2019)[130]	0.5	0-2	73	Low-grade AVMs
Kocer et al. (2019)[238]	0.5	0-2	31	High-grade, SM III-V AVMs
Jean et al. (2019)[239]	1.6	0-1	86	90% lobar AVMs
Madhugiri et al. (2018)[122]	4.0	0-2	39	Brainstem AVMs
Hung et al. (2018)[240]	3.0	0-1	137	SMG II AVMs
Pohjola et al. (2018)[121]	9.7	0-2	38	Posterior fossa AVMs
Mascitelli et al. (2018)[123]	2.0	0-2	241	Eloquently located AVMs
Lin et al. (2017)[237]	1.6	0-2	184	39% eloquently located AVMs
Schramm et al. (2017)[50]	5.3	0-1	288	Cerebral AVMs
Morgan et al. (2017)[119]	1.0	0-1	675	SMG I-III AVMs
Bervini et al. (2017)[241]	1.0	0-1	769	87% supratentorial
Tong et al. (2017)[120]	6.4	0-2	181	Cerebellar AVMs
Javadpour et al. (2016)[85]	0.5	0-1	45	Unruptured AVMs
Potts et al. (2015)[118]	1.7	0-1	232	SMG I-II AVMs
Han et al. (2015)[86]	1.3	0-2	27	Brainstem AVMs

6 DISCUSSION

6.1 The long-term HRQoL in AVM patients in general is favorable

After severe illness, it is not self-evident that the patient can return to the pre-morbid lifestyle or adjust to the changes in the postmorbid condition. This is especially true for the young, working-age AVM patients, who are usually without pre-existing comorbidities during their diagnosis. Taking these factors into consideration, after long-term follow-up the HRQoL results in general were only modestly impaired when compared to the general population.[I,III] Interestingly, certain subgroups, such as mRS 0 AVM patients had even better subjective HRQoL than the general population controls.[III] The factors associated with decreased HRQoL in the multivariate model were older age, sex (female), refractory epilepsy, SPC C type lesion and more than one bleeding episode.[I] Also, understandably, poor functional status decreased the HRQoL in long-term follow-up.[I,III] The decrease in the ability to continue previous usual activities was a major component explaining the impaired HRQoL.[I,III] This dimension is one of the key elements creating postmorbid happiness and life satisfaction.[230, 242] Despite this, only a few had had to retire from their work owing to the AVM, illustrating at least some capability to continue the previous lifestyle.[I] Return to work is a well-recognized component of postmorbid QoL and life satisfaction in patients with SAH and ICH.[230, 243] Mental functioning, another important factor affecting postmorbid HRQoL,[228, 229] was impaired only in patients with refractory, symptomatic epilepsy and SPC C lesions.[I] This decrease has previously been explained with possible damage to the reticular formation and related structures of the brain controlling arousal, and it has been associated with sleeping disorders, stress, pain and chronic illnesses in SAH and IS patients.[230, 231] However, given the decrease epilepsy has on HRQoL independently based on previous studies,[58] it is possible that the anticonvulsive medicine and factors related to the epilepsy itself affect the HRQoL substantially more than these theoretical changes in the parenchyma owing to AVM hemorrhage. However, the magnitude in which these factors independently affect postmorbid HRQoL cannot be differentiated by our results.

6.2 Treatment decisions

ARUBA managed to turn the treatment policies of AVM patients into a more conservative course. It has sparked vigorous conversation in the neurosurgical community about the risks of interventional treatment, and on the other hand the risks of watchful waiting. SPC B patients have been the

borderline group regarding treatment recommendations. According to our results, the long-term HRQoL was relatively similar between SPC A (who are generally considered safe for surgery) and SPC B patients.[I] Taking into account the effect multiple bleeding episodes had on HRQoL, our results carefully suggest that interventional treatment can yield as successful results in SPC B patients as in SPC A patients.[I] Direct treatment recommendations cannot be given, however, without a conservative control group. Furthermore, the variability of lesion anatomy inside the SPC B category should be considered. Therefore, the importance of careful evaluation of treatment possibilities in light of the features of the AVM, preferably by an interdisciplinary team, is extenuated in this patient group. Our long-term HRQoL results do not question the role of microsurgery as the gold standard for SPC A patients. However, mirroring the decreased HRQoL of treated SPC C patients, it is still advisable to remain conservative at least until progressive neurological symptoms begin to develop or the lesion bleeds. Again, without a control group, we cannot tell what the HRQoL of these patients would have been with a conservative treatment policy. The survival bias associated with our long follow-up time could optimize the results for these patients, as well as the other groups included in our studies. There was a significant decrease of HRQoL in the patients with symptomatic refractory epilepsy (Engel II–IV).[I] Therefore, complete seizure-freedom also creates another meaningful treatment goal in the sense of postoperative HRQoL.

6.3 Dichotomous mRS

The subjectivity of ''good'' and ''bad'' creates difficulties in the analysis, reporting and interpretation of outcome. Some minor postoperative symptoms might be accepted if the patient was doing worse off preoperatively, whereas, for an asymptomatic patient the same symptoms might represent a significant decrease in HRQoL. Objective outcome instruments, such as mRS, are needed in the transparent comparison of treatment strategies, patients and institutions. As an objective outcome instrument, this phenomenon based on subjectivity should not affect the evaluation of the mRS. However, with an increasing interest in HRQoL, and the increased use of utility-weighted mRS in the scientific community, we wanted to explore the interconnected relationship of the objective mRS and the subjective HRQoL measured with 15D. Given that mRS is meant to demonstrate the ability to continue previous usual activities and functional in/dependence, these factors were translated into the subjective HRQoL, with the exception of overlap between mRS 1 and mRS 2 patients in the dimension of usual activities.[III] Despite this connection between objective and subjective outcome, the determining of unfavorable and favorable mRS remains difficult because many aspects of HRQoL were not illustrated by mRS.[III] The psychological and mental dimensions, major components of life satisfaction, were not differentiated between the grades.[III] In contrast, differences in these dimensions were demonstrated in the first

study of this thesis, suggesting that this was not owing to the inability of the 15D to capture the differences.[I] This is one of the many reasons why the arbitrary division of mRS into ''good'' and ''bad'' should be avoided. Furthermore, since in real life we are interested in the improvement or decline of a patient's condition, should not the methodology be set so that it could capture these movements across the scale?

6.4 Differences between AVM patients in mRS 0 and 1

Dichotomizing has been and is still common in neurological and neurosurgical research. Therefore, understanding the effect it has on research results is essential. With our literature review, we illustrated that the two most common cut points used in the recent neurosurgical literature are between mRS 1 and 2, and 2 and 3.[III] Both of these options have also been the common alternatives in many stroke trials and neurological research. Our results that mRS 0 and mRS 1 have a significantly different long-term HRQoL, and on the other hand that mRS 1 and 2 patients had a relatively similar HRQoL, clash against the inclusion of mRS 0 and 1 patients into the same category of ''favorable'' outcome.[III] However, these results are against the recent findings of two meta-analyses using the EQ-5D HRQoL instrument, in which mRS 0 and mRS 1 stroke patients were regarded as close in utility weights.[244, 245] Compared to 15D, EQ-5D has been reported to have a higher ceiling effect, meaning that the improvement in HRQoL with patients in the best possible health states might remain undetected because the scale runs out.[246] Also, the aforementioned meta-analyses have investigated mostly IS patients. The different biology behind the diseases could explain why, despite being classified similarly in regard to functioning, the rest of the dimensions differ significantly.

So based on our results, it seems that the inclusion of mRS 0 and mRS 1 in the same category might overly optimize the results for mRS 1 patients in AVM research.[III] Additionally, dichotomizing between mRS 1 and 2 creates an artificial boundary between the patients, when in fact they seem to be close in long-term HRQoL.[III] Whether these findings apply to other causes of ICH is a subject for future research. Some of the extreme improvement in the HRQoL of mRS 0 patients compared to the general population might be explained by the fact that it could be difficult for the control individuals to estimate their common symptomatology compared to patients who have possibly experienced real disabling symptoms. However, this same phenomenon also exists with the control individuals in the mRS 1 comparison, and thus does not explain the difference between mRS 0 and mRS 1 patients.

Even if we got rid of mRS dichotomization in future research, it should be noted that the gaps between mRS grades are not identical in distance, meaning that a drop in functional outcome from mRS 1 to mRS 2 does not change the HRQoL as much as the drop from mRS 0 to mRS 1. Furthermore, in real life the starting point of the patient plays a major role in the interpretation of the outcome,

since for an asymptomatic patient with an unruptured lesion the outcome of mRS 1 might be a catastrophe, whereas for an unconscious patient after a massive AVM hemorrhage the same outcome could be regarded as phenomenal. Further analyses of these different scenarios are needed, as well as results from other patient populations to widen our understanding of the mRS and to improve our future research.

6.5 The prevalence of smokers in AVM patients

Researchers have long suggested the two-hit theory behind the formation of AVMs.[44] Yet, no external pathogens had reliably been linked to AVM patients before our findings.[II] Neither the causality nor the exact relationship between smoking and AVM patients can be discovered by our results, however, the high prevalence of smokers during the diagnosis of AVM could suggest a role in either provoking the rupture or behind the etiology. It is safe to say that smoking cessation should be recommended to all patients with cerebrovascular diseases, including AVM patients. This is also supported by the finding that smoking can decrease the likelihood of AVM obliteration.[185] Whether the trend of less smoking in the 2000s and presumably in the future decreases the rupture rates is another interesting topic of future research. There has already been a slight decrease in the incidence of new AVMs in our clinic, however, the exact trend will only be illustrated during the years to come. It is possible, given the interconnected relationship of many notorious lifestyle factors, that there are other modifiable risk factors yet to be discovered. Another well-known cerebrovascular risk factor, hypertension, was linked to hemorrhagic presentation of AVM patients already in 1998,[182] however, these results have not been replicated in other patient cohorts ever since. Whether this is owing to the difficulty in the methodologies or the lack of underlying connection between AVM patients and hypertension, cannot be determined based on current knowledge. We hope our findings spark the exploration of AVM patient cohorts, since the confirmation of this connection between smoking and AVM patients could be the key factor in determining the etiology and future treatment of AVMs.

6.6 Future aspects

The on-going exploration of AVM pathogenesis opens up new possibilities for novel medical therapies. The connection we found between AVM patients and smoking is well-suited to these theories about the importance of VEGF and other vascular endothelial markers in the pathogenesis of AVMS.[II] Even before the finding of KRAS mutations in somatic AVMs,[7] there have been few phase 1 trials on the pharmaceutical possibilities in treating AVM patients. Anti-VEGF drugs have been proposed as a future treatment. There is one phase 1 clinical trial (NCT02314377) investigating the safety and effectiveness of bevacizumab (VEGF-A inhibitor), which ended in

December 2019, however, results are yet unpublished. The tetracycline derivates such as minocycline and doxycycline (MMP-9 inhibitors) have also been investigated and deemed feasible in phase 1 for future trials.[247] A phase 2 trial (NCT04297033) investigating lovastatin is currently on-going and is estimated to be completed in 2024. The mechanism of action is proposed to be in the stabilizing, anti-inflammatory and antiproliferative, effect of statins on the endothelium. These medical therapies are of special importance to those patients currently out of possibilities regarding interventional methods. However, given the majority of patients are diagnosed with already ruptured AVMs, the need for interventional methods is not likely to be diminishing in the near future. Therefore, discovering the risk factors behind AVM formation and in this way catching these lesions before they rupture is the next major challenge in AVM research.

Studies on the HRQoL of AVM patients will help clinicians together with the patients contemplate the risks of interventional treatment methods against the risks of conservative management. Understanding the outcome in more detail than just the functionality or independence will help focus resources on the aspects needing rehabilitation or intervention. There is a new on-going clinical trial for the treatment of brain AVMs (TOBAS, NCT02098252), however, it has not reported a HRQoL outcome nor as a primary nor secondary outcome. Still, its results will help in understanding the results of ARUBA, however, it will take many years still to complete. Until then, understanding HRQoL will give us new information about AVM patients and therefore becomes especially important in the discussion about treatment strategies.

Finland is well-suited for epidemiological studies owing to its nation-wide registries and public healthcare system, in which all AVM patients are treated in university hospitals. An interesting idea for future research would be to use these national healthcare registries to track the condition of the patients who did not answer the HRQoL questionnaire sent in 2016. To apply this even further, a nation-wide AVM registry could be collected using the data derived from the Finnish Institute for Health and Welfare (THL), Kela (social insurance institution) and the Kanta (social and healthcare services) registries. These systems allow researchers access to electronic prescriptions, rehabilitation benefits and disability pension data, in addition to numerous other important factors in understanding the comorbidities, lifestyle, functional outcome and QoL of AVM patients.

6.7 Limitations

The long follow-up time causes at least some magnitude of survival bias, which optimizes our results by excluding those not well enough to answer or to survive long enough to attend the survey. This has to be considered, especially with the patients with the SPC C lesions, multiple bleeding episodes and deeply located AVMs. Additionally, owing to the small number of patients treated with either only embolization or SRS, comparisons

between treatment modalities could not be conducted.

Study II was limited by its cross-sectional nature, as this design of study cannot prove causality. Also, many AVM patients had left some parts of the HRQoL questionnaire unanswered, which led to classifying them as nonsmokers to obtain a conservative estimate about the prevalence of smokers. Therefore, the real prevalence could be higher than we reported. On the other hand, smoking was common in the previous millennium, which might cause overestimation, however, this was taken into account by controlling for the general population with age group, sex and admission year. Finally, owing to the relative homogeneity of the Finnish population, our results are not generalizable to other nationalities. Therefore, we encourage other research groups to study their patient populations to understand whether these phenomena appear globally.

7 CONCLUSION

The research papers of this thesis project reported novel findings about the risk factors for decreased HRQoL in long-term follow-up, the possible underlying lifestyle risk factors of AVM patients and the methodological risks the common use of mRS dichotomization might pose. In the post-ARUBA era, our results were able to support the active treatment of selected SPC B patients by showing favorable HRQoL outcomes after a total obliteration of the AVM and to remain conservative with SPC C patients. The HRQoL results illustrated that there is room for improvement regarding the postoperative treatment of AVM patients, as many of them suffer from impairments of mental health and decreased ability to continue previous activities, even decades after the incidence. Still, the overall outcome of AVM patients was rather favorable, when considering the severity of the disease and the outcomes of the patients with other causes of intracranial hemorrhage. The finding of the association between cigarette smoking and AVM patients inspires more vigorous investigation of the currently unknown etiology of AVMs. Understanding the etiology could open up new possibilities for prevention and medical therapies in AVM treatment. Finally, our results revealed that the dichotomous analysis of the mRS in the outcome analyses should be critically re-evaluated, as there could be considerable differences in the postoperative outcomes of mRS 0 and mRS 1 patients. None of these findings were possible without the application of the patient-reported outcome evaluation, the use of modern HRQoL instruments and the help of my instructors and co-writers.

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Today as I'm writing this final part of my dissertation, the covid-19 pandemic has been disturbing our daily lives for one (longer than usual) year. Although we are starting to see light at the end of the tunnel, owing to the current situation, it saddens me not to be able to invite professor **Karl Schaller** to Helsinki. I'm so grateful and honored for your agreement to be my opponent in the thesis defense. I truly hope we can soon meet in person.

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In Helsinki,
February 2021
Anni Pohjola

APPENDICES

Appendix 1: The 15D questionnaire. Patients are asked to fill in the option that best describes their current health status.

QUESTION 1. MOBILITY	
1 ( )	I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2 ( )	I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( )	I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( )	I am able to walk indoors only with help from others.
5 ( )	I am completely bed-ridden and unable to move about.
QUESTION 2. VISION	
1 ( )	I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( )	I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( )	I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( )	I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
5 ( )	I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.
QUESTION 3. HEARING	
1 ( )	I can hear normally, i.e. normal speech (with or without a hearing aid).
2 ( )	I hear normal speech with a little difficulty.
3 ( )	I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.
4 ( )	I hear even loud voices poorly; I am almost deaf.
5 ( )	I am completely deaf.
QUESTION 4. BREATHING	
1 ( )	I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
2 ( )	I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3 ( )	I have shortness of breath when walking on flat ground at the same speed as others my age.
4 ( )	I get shortness of breath even after light activity, e.g. washing or dressing myself.
5 ( )	I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING	
1 ( )	I am able to sleep normally, i.e. I have no problems with sleeping.
2 ( )	I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
3 ( )	I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
4 ( )	I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5 ( )	I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.
QUESTION 6. EATING	
1 ( )	I am able to eat normally, i.e. with no help from others.
2 ( )	I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
3 ( )	I need some help from another person in eating.
4 ( )	I am unable to eat by myself at all, so I must be fed by another person.
5 ( )	I am unable to eat at all, so I am fed either by tube or intravenously.
QUESTION 7. SPEECH	
1 ( )	I am able to speak normally, i.e. clearly, audibly and fluently.
2 ( )	I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
3 ( )	I can make myself understood, but my speech is e.g. disjointed, faltering, stuttering or stammering.
4 ( )	Most people have great difficulty understanding my speech.
5 ( )	I can only make myself understood by gestures.
QUESTION 8. EXCRETION	
1 ( )	My bladder and bowel work normally and without problems.
2 ( )	I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
3 ( )	I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhea.
4 ( )	I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.
5 ( )	I have no control over my bladder and/or bowel function.
QUESTION 9. USUAL ACTIVITIES	
1 ( )	I am able to perform my usual activities (e.g. employment, studying, housework, free-time activities) without difficulty.
2 ( )	I am able to perform my usual activities slightly less effectively or with minor difficulty.
3 ( )	I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
4 ( )	I can only manage a small proportion of my previously usual activities.
5 ( )	I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION	
1 ( )	I am able to think clearly and logically, and my memory functions well
2 ( )	I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3 ( )	I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4 ( )	I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
5 ( )	I am permanently confused and disoriented in place and time.
QUESTION 11. DISCOMFORT AND SYMPTOMS	
1 ( )	I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
2 ( )	I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
3 ( )	I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
4 ( )	I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
5 ( )	I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
QUESTION 12. DEPRESSION	
1 ( )	I do not feel at all sad, melancholic or depressed.
2 ( )	I feel slightly sad, melancholic or depressed.
3 ( )	I feel moderately sad, melancholic or depressed.
4 ( )	I feel very sad, melancholic or depressed.
5 ( )	I feel extremely sad, melancholic or depressed.
QUESTION 13. DISTRESS	
1 ( )	I do not feel at all anxious, stressed or nervous.
2 ( )	I feel slightly anxious, stressed or nervous.
3 ( )	I feel moderately anxious, stressed or nervous.
4 ( )	I feel very anxious, stressed or nervous.
5 ( )	I feel extremely anxious, stressed or nervous.
QUESTION 14. VITALITY	
1 ( )	I feel healthy and energetic.
2 ( )	I feel slightly weary, tired or feeble.
3 ( )	I feel moderately weary, tired or feeble.
4 ( )	I feel very weary, tired or feeble, almost exhausted.
5 ( )	I feel extremely weary, tired or feeble, totally exhausted.
QUESTION 15. SEXUAL ACTIVITY	
1 ( )	My state of health has no adverse effect on my sexual activity.
2 ( )	My state of health has a slight effect on my sexual activity.
3 ( )	My state of health has a considerable effect on my sexual activity.
4 ( )	My state of health makes sexual activity almost impossible.
5 ( )	My state of health makes sexual activity impossible.

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